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Endosulfan: Ambient Water Quality Criteria

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ENDOSULFAN

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for endosulfan.

KEYWORDS: *Water quality, *Toxicology, *Toxic substances, *Water pollution effects(Humans), *Endosulfan.

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CRITERION DOCUMENT

ENDOSULFAN

CRITERIA

Aquatic Life

For endosulfan the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.042 µg/l as a 24-hour average and the concentration should not exceed 0.49 µg/l at any time.

For saltwater aquatic life, no criterion for endosulfan can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of endosulfan ingested through water and contaminated aquatic organisms, the ambient water criterion is 0.1 mg/l.

Introduction

Endosulfan is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. It was discovered and developed in 1954 by Farbwerke Hoechst AG. in Germany and introduced under the registered trademark Thiodan. The trade names of endosulfan include Beosit, Chlorthiepin, Cyclodan, Insectophene, Kop-Thiodan, Malix, Thifor, Thimul, Thioden, and Thionex (Berg, 1976).

Annual production of endosulfan in the United States was estimated in 1974 at three million pounds. It is presently on the Environmental Protection Agency's restricted list which limits its usage. However, significant commercial use of endosulfan for insect control on vegetables, fruits, and tobacco continues.

Endosulfan has been demonstrated to be highly toxic to fish and marine invertebrates and is readily adsorbed by sediments. It therefore represents a potential hazard in the aquatic environment.

Endosulfan is a light to dark brown crystalline solid with a terpene-like odor, having the molecular formula $C_9Cl_6H_6O_3S$, a molecular weight of 406.95, and a vapor pressure of 9×10^{-3}mm Hg at 80°C (Brooks, 1974; Whetstone, 1972). It exhibits a solubility in water of 60 to 150 µg/l and is readily soluble in organic solvents (Braun and Frank, 1973). The chemical name for endosulfan is 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-

oxide. It is prepared through the Diels-Adler addition of hexachlorocyclopentadiene with cis-butene-1,4-diol to form the bicyclic dialcohol, followed by esterification and cyclization with $SOCl_2$ (Windholz, 1976).

Technical grade endosulfan has a purity of 95 percent and is composed of a mixture of two steroisomers referred to as alpha and beta or I and II. It has a melting point range of 70 to 100°C and a density of 1.745 at 20°C (Burchfield and Johnson, 1965). The endosulfan isomers are present in the ratio 70 percent isomer I to 30 percent isomer II. Impurities present in technical grade endosulfan consist mainly of the degradation products and may not exceed two percent endosulfandiol and one percent endosulfan ether. Endosulfan is commercially available in the form of wettable powders, emulsifiable concentrates, granules, and dusts of various concentrations (Berg, 1976). It is a powerful contact and stomach insecticide used to control a wide spectrum of insects.

Endosulfan is stable to sunlight, but is susceptible to oxidation and the formation of endosulfan sulfate in the presence of growing vegetation (Cassil and Drummond, 1965). Technical grade endosulfan is sensitive to moisture, bases, and acids and decomposes slowly by hydrolysis to SO_2 and endosulfan alcohol.

In the environment, endosulfan is metabolically coverted by microorganisms, plants, and animals to endosulfan sulfate, endosulfandiol, endosulfan ether, endosulfan hydroxyether, and endosulfan lactone (Martens, 1976; Chopra and Mahfouz, 1977; Gorbach, et al. 1968). Of these conversion products, endosulfan sulfate is of toxicologic importance.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Endosulfan is a broad spectrum chlorinated cyclodiene insecticide. Although restrictions on the use of endosulfan in the United States have been proposed, significant commercial use continues for insect control on vegetables, fruits, alfalfa, and tobacco. Most of the acute studies were carried out under static conditions and with unmeasured concentrations. For most of these studies technical-grade endosulfan or formulations containing technical endosulfan were used. Technical-grade endosulfan is a 94- to 96-percent mixture of stereo isomers, endosulfan I and II, in a ratio of 70:30. Toxicity of the isomers may be different, but insufficient data are available to determine which isomer is more toxic and the relative toxicity of the two isomers may vary with the species tested. Data reported herein, except for the Final Plant Value, were based on tests using technical-grade endosulfan. Tests using formulations such as emulsifiable concentrates were not used because of possible effects of other components of the formulation.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Two studies were conducted on the effect of temperature on endosulfan toxicity, and one study was conducted on the effect of water hardness (Macek, et al. 1969; Schoettger, 1970a; Pickering and Henderson, 1966). In general, based on the limited data, toxicity increased with increasing temperature but hardness had no effect.

One invertebrate and one fish chronic test have been conducted (Macek, et al. 1976). No measured steady-state freshwater bioconcentration test data are available, and only one value for a plant effect is available.

Acute Toxicity

Static tests were conducted in all but one study (Macek, et al. 1976) (Table 6). In only one of the static tests was the concentration of endosulfan measured (Herzel and Ludemann, 1971) (Table 6). Values for the standard tests with fish and invertebrate species are given in Tables 1 and 2.

In general, fish were more sensitive to endosulfan than invertebrate species. Adjusted LC50 values for fish ranged from 0.2 µg/l for rainbow trout, to 4.9 µg/l for carp (Table 1). Adjusted LC50 values for invertebrate species ranged from 1.9 µg/l for the stonefly, Pternoarcys californica, to 140.6 µg/l for the cladoceran, Daphnia magna (Table 2).

Several of the authors, cited in Tables 1 and 2, reported values for other pesticides in addition to endosulfan. For fish, endosulfan was second in toxicity only to endrin in acute studies with both organophosphate and organchlorine insecticides (Macek, et al. 1969; Ludemann and Neumann, 1960). For invertebrate species, endosulfan had medium toxicity among the chlorinated hydrocarbon insecticides. Sanders (1972 and 1969) found endosulfan to be less toxic than DDT and endrin, but more toxic than lindane, toxaphene, chlordane, heptachlor, and dieldrin for two species of scud, Gammarus fasciatus and Gammarus lacustris. Sanders and Cope (1968) found somewhat different results for the stonefly. Endosulfan was less toxic than endrin, dieldrin, and heptachlor, but more toxic than lindane, DDT, and chlordane. Toxaphene had toxicity similar to endosulfan. Ludemann and Neumann (1962) found endosulfan less toxic than DDT and chlordane, but more toxic than heptachlor for the midge, Chironomus plumosus. Lindane was similar in toxicity to endosulfan.

For fish, endosulfan was consistently one of the most toxic pesticides tested. For invertebrate species, it is difficult to determine how much of the variation in the results of toxicity tests with the different pesticides is due to species sensitivity or test variation.

Pickering and Henderson (1966) studied the effect of water hardness on toxicity of endosulfan and observed no significant effect. Unadjusted 96-hour LC50 values for the bluegill exposed to technical-grade endosulfan in soft and hard water were 3.3 µg/l and 4.4 µg/l, respectively.

In contrast to the effect of hardness, toxicity of endosulfan generally increased with increasing temperature. Macek, et al. (1969) found an increase in toxicity to rainbow trout when tested at 7.2 and 12.7°C as compared to 1.6°C (Table 1). Schoettger (1970b) found that endosulfan toxicity increased with temperature for rainbow trout tested at 10°C as compared to 1.5°C. He also found that endosulfan toxicity increased with temperature for white sucker, and Daphnia magna when tested at 19°C compared to 10°C. The only exception was the damselfly, Ischura sp., which showed decreased toxicity when tested at 19°C as compared to 8°C (Table 2). Although not shown in the tables, the differences in toxicity with temperature were usually greater at 24 hours than at 96 hours.

Several authors reported LC50 values for fish after 24-, 48-, and 96-hours exposure to endosulfan. In general, they found toxicity increased slightly with time but considerable differences between species existed, however.

For fish, the ratio of 96-hour/24-hour and 96-hour/48-hour LC50 values ranged from 0.13 to 0.95 and from 0.27 to 1.00, respectively. The geometric means of the ratios grouped by species were 0.51 for the 96-hour/24-hour LC50 value and 0.66 for the 96-hour/48-hour LC50 value. These ratios are approximately 20 percent less than the Guidelines values (0.66 and 0.81 for adjustment of 24-hour and 48-hour LC50 values, respectively). Considering the variation and the limited number of data points (four), the ratios are reasonably close to the Guidelines values. The Guidelines value (0.81) was used for the one fish LC50 value (Table 1) that required adjustment.

For invertebrate species, the ratio of 96-hour/24-hour LC50 values and 96-hour/48-hour LC50 values ranged from 0.09 to 0.63 and from 0.41 to 0.91, respectively. The geometric means for the 96-hour/24-hour LC50 values and for the 96-hour/48-hour LC50 values were 0.38 and 0.61, respectively. Considering the variation and limited number of data points (four), the values are reasonably close to the Guidelines values of 0.26 and 0.61.

The absence of flow-through tests with measured concentrations is primarily a function of the technology and state-of-the-art of aquatic toxicology at the time when much of the testing was done. Measurements of test concentrations and flow-through test procedures would probably give better data on the acute toxicity of endosulfan for aquatic organisms. Herzel and Ludemann (1971) (Table 6) studied the effect of test conditions on the results of static tests. They found greater than a 6-fold decrease in the measured concentrations of endosulfan at the end of a 96-hour static, unaerated exposure and greater than a 40-fold decrease in an aerated test compared to the initial concentration at the start of the test. These results indicate the potential problem of determining the effective exposure concentration in static tests.

There are no data on side-by-side comparisons of static and flow-through tests with measured concentration of endosulfan. Macek, et al. (1976) (Table 6), however, determined 0.86 µg/l endosulfan to be the incipient lethal level for fathead minnows. The test was a seven-day flow-through test with measured concentrations. The incipient lethal level from that test for the fathead minnow was greater than 3 of the 5 adjusted 96-hour values for rainbow trout (Table 1). Rainbow trout was the most sensitive species tested. No other data were available for comparison of static and flow-through tests and tests with measured concentrations. The Guidelines values were used for all static and unmeasured concentration adjustments of fish tests.

Final Fish and Final Invertebrate Acute Values were derived using values listed in Tables 1 and 2. The LC50 values from the literature were adjusted using the Guidelines procedures to be equivalent to 96-hour, flow-through toxicant-measured LC50 values. The final acute values were calculated according to the Guidelines and were 0.49 µg/l for fish and 0.60 µg/l for invertebrate species. Therefore, the Final Acute Value is 0.49 µg/l.

Chronic Toxicity

The only available fish chronic study was that of Macek, et al. (1976) with the fathead minnow (Table 3). The test lasted 40 weeks, and growth, survival, and reproduction were monitored. Based on no adverse effects on parental fish or offspring at 0.20 µg/l and observed poor hatchability of control eggs hatched in

0.40 μg/l endosulfan, the maximum acceptable endosulfan concentration for fathead minnows was between 0.20 and 0.40 μg/l.

Since there are no measured, acute 96-hour flow-through fathead minnow data, there is no way to determine an application factor. Acute toxicity data, however, indicate the fathead minnow may not be the most sensitive species. The Guidelines sensitivity factor was, therefore, used to calculate the Final Fish Chronic Value, 0.042 μg/l.

Chronic data for *Daphnia magna* are available from the study of Macek, et al. (1976). Based on effects of endosulfan on survival of *Daphnia magna* through the first two generations, the maximum acceptable concentration of endosulfan was between 2.7 and 7.0 μg/l. As with acute toxicity, the invertebrate species would appear to be less sensitive to chronic endosulfan toxicity than fish. It should be noted, however, that *Daphnia magna* in the acute tests was one of the less sensitive invertebrate species to endosulfan toxicity. The Guidelines sensitivity factor was used to calculate the Final Invertebrate Chronic Value which is 0.84 μg/l (Table 4).

Plant Value

The only plant-effect data was obtained from a study by Gorback and Schulze (1973). In that study growth of the green alga, *Chlorella vulgaris*, was inhibited at concentrations greater than 2,000 μg/l (Table 5). Since this is the only plant value, the Final Plant Value is 2,000 μg/l.

Residues

No acceptable bioconcentration studies with endosulfan were conducted with freshwater fish. Because endosulfan is a chlorinated cyclodiene insecticide and other members of that group of insecticides bioconcentrate, data for accumulation of endosulfana by freshwater fish and invertebrate species would be useful for more complete development of criteria. Data on saltwater organisms indicate endosulfan does concentrate up to 1,597 times (see Saltwater section).

Miscellaneous

Other data for effects of endosulfan are listed in Table 6.or None of the data in these studies indicate that the final acute chronic values calculated for endosulfan are inappropriate.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 0.49 μg/l

Final Invertebrate Acute Value = 0.60 μg/l

Final Acute Value = 0.49 μg/l

Final Fish Chronic Value = 0.042 μg/l

Final Invertebrate Chronic Value = 0.84 μg/l

Final Plant Value = 2,000 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 0.042 μg/l

0.44 x Final Acute Value = 0.22 μg/l

The maximum concentration of endosulfan is the Final Acute Value of 0.49 μg/l and the 24-hour average concentration is the Final Chronic Value of 0.042 μg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For endosulfan the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.042 μg/l as a 24-hour average and the concentration should not exceed 0.49 μgl at any time.

Table 1. Freshwater fish acute values for endosulfan

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	S	U	Technical grade	96	2.6	1.4	Macek, et al. 1969
Rainbow trout, *Salmo gairdneri*	S	U	Technical grade	96	1.7	0.9	Macek, et al. 1969
Rainbow trout, *Salmo gairdneri*	S	U	Technical grade	96	1.5	0.8	Macek, et al. 1969
Rainbow trout, *Salmo gairdneri*	S	U	Technical grade	96	0.8	0.4	Schoettger, 1970
Rainbow trout, *Salmo gairdneri*	S	U	Technical grade	96	0.3	0.2	Schoettger, 1970
Carp (fingerling), *Cyprinus carpio*	S	U	Technical grade	48	11.0	4.9	Lüdemann & Neumann, 1960
White sucker, *Catostomus commersoni*	S	U	Technical grade	96	3.5	1.9	Schoettger, 1970
White sucker, *Catostomus commersoni*	S	U	Technical grade	96	3.0	1.6	Schoettger, 1970
Guppy, *Poecilia reticulata*	S	U	Technical grade	96	3.7	2.0	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S	U	Technical grade	96	3.3	1.8	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S	U	Technical grade	96	4.4	2.4	Pickering & Henderson, 1966

* S = static

** U = unmeasured

Geometric mean of adjusted values = 1.9 µg/l $\frac{1.9}{3.9}$ = 0.49 µg/l

Table 2. Freshwater invertebrate acute values for endosulfan

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, *Daphnia magna*	S	U	Technical grade	48	166.0	140.6	Macek, et al. 1976
Cladoceran, *Daphnia magna*	S	U	Technical grade	48	132.0	111.8	Schoettger, 1970
Cladoceran, *Daphnia magna*	S	U	Technical grade	48	62.0	52.5	Schoettger, 1970
Scud, *Gammarus fasciatus*	S	U	Technical grade	96	6.0	5.1	Sanders, 1972
Scud, *Gammarus lacustris*	S	U	Technical grade	96	5.8	4.9	Sanders, 1969
Stonefly (naiad), *Pteronarcys californica*	S	U	Technical grade	96	2.3	1.9	Sanders & Cope, 1968
Damselfly (naiad), *Ischura sp.*	S	U	Technical grade	96	71.8	60.8	Schoettger, 1970
Damselfly (naiad), *Ischura sp.*	S	U	Technical grade	96	107.0	90.6	Schoettger, 1970

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* S = static

** U = unmeasured

Geometric mean of adjusted values = 12.7 µg/l $\frac{12.7}{21}$ = 0.60 µg/l

Table 3. Freshwater fish chronic values for endosulfan (Macek, et al. 1976)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, *Pimephales promelas*	LC	0.20-0.40	0.28

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* LC = life cycle or partial life cycle

Geometric mean of chronic values = 0.28 µg/l $\frac{0.28}{6.7}$ = 0.042 µg/l

Lowest chronic value = 0.28 µg/l

Table 4. Freshwater invertebrate chronic values for endosulfan (Macek, et al. 1976)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Cladoceran, *Daphnia magna*	LC	2.7-7.0	4.3

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* LC = life cycle or partial life cycle

Geometric mean of chronic values = 4.3 µg/l $\frac{4.3}{5.1} = 0.84$ µg/l

Lowest chronic value = 4.3 µg/l

Table 5. Freshwater plant effects for endosulfan (Knauf & Schulze, 1973)

Organism	Effect	Concentration (ug/l)
Green alga, *Chlorella vulgaris*	Inhibited growth in 120-hrs test	> 2,000 Endosulfan 35 EC

Lowest plant value = 2,000 µg/l

Table 6. Other freshwater data for endosulfan

Organism	Test Duration	Effect	Result (ug/l)	Reference
Midge (larva), Chironomus plumosus	24 hrs	LC50	53	Lüdemann & Neumann, 1962
Rainbow trout (fry), Salmo gairdneri	24 hrs	100% mortality	10	Lüdemann & Neumann, 1961
Northern pike (fingerling), Esox lucius	24 hrs	100% mortality	5	Lüdemann & Neumann, 1961
Fathead minnow, Pimephales promelas	7 days	Incipient LC50	0.86	Macek, et al. 1976
Carp, Cyprinus carpio	24 hrs	70% mortality, 2% emulsifiable concentrate	10	Mulla, et al. 1967
Carp, Cyprinus carpio	24 hrs	60% mortality in cages submerged in ponds dosed with Endosulfan 2% emulsifiable concentrate	25	Mulla, et al. 1967
Mosquitofish, Gambusia affinis	24 hrs	6% mortality in cages submerged in ponds dosed with Thiodan® I, 2% emulsifiable concentrate	0.1 lbs/acre	Mulla, 1963
Mosquitofish, Gambusia affinis	24 hrs	24% mortality in cages submerged in ponds dosed with Thiodan® II, 2% emulsifiable concentrate	0.1 lbs/acre	Mulla, 1963
Guppy, Poecilia reticulata	5 hrs	100% mortality	50	Jones, 1975
Guppy, Poecilia reticulata	96 hrs	85% mortality in unaerated static test, technical grade	4.2	Herzel & Lüdemann, 1971

Table 6. (Continued) --

Organism	Test Duration	Effect	Result (ug/l)	Reference
Guppy, *Poecilia reticulata*	96 hrs	55% mortality in aerated static test, technical grade	4.2	Herzel & Lüdemann, 1971
Bluegill, *Lepomis macrochirus*	Unspecified	50% inhibition of brain mitochondrial Mg - ATPase	6,050	Yap, et al. 1975
Bullfrog (tadpole), *Rana catesbeiana*	24 hrs	60% mortality in cages submerged in ponds dosed with Thiodan® I, 2% emulsifiable concentrate	0.1 lbs/acre	Mulla, 1963
Bullfrog (tadpole), *Rana catesbeiana*	96 hrs	10% mortality in cages submerged in ponds dosed with Thiodan® II, 2% emulsifiable concentrate	0.1 lbs/acre	Mulla, 1963
Tubificid worm, *Tubifex tubifex*	96 hrs	100% mortality	10,000	Lüdemann & Neumann, 1962
Mallard (young), *Anas platyrhynchus*	5 days	50% mortality	1,050 mg/kg	Hill, et al. 1975

SALTWATER ORGANISMS

Introduction

The organochlorine insecticide, endosulfan, has been used for many years to control pests that infest a wide spectrum of fruits and vegetables. Technical endosulfan is composed of two stereoisomers, endosulfan I and II, in the approximate ratio of 70:30. Both isomers are readily metabolized to endosulfan sulfate by a wide variety of organisms (Maier-Bode, 1968).

The acute toxicity of endosulfan to saltwater fishes and crustaceans was documented as early as 1963 (Butler, 1963). No chronic studies have been conducted on saltwater animals; however, several bioconcentration studies were conducted in the mid-1970's (Roberts, 1972, 1975; Schimmel, et al. 1977).

Acute Toxicity

Saltwater fishes exposed to endosulfan exhibited toxic effects at concentrations below 1 µg/l (Table 7). Of the five species tested, the unadjusted 48- or 96-hour LC50 values ranged from 0.09 to 0.6 µg/l (Butler, 1963, 1964; Korn and Earnest, 1974; Schimmel, et al. 1977). With the exception of rainbow trout (Salmo gairdneri), freshwater fishes were not as sensitive in acute tests (Table 1).

The seven saltwater invertebrate species tested were highly disparate in sensitivity to endosulfan (Table 8). The range of unadjusted EC50 and LC50 values was from 0.04 to 380 µg/l. The least sensitive invertebrate species was the eastern oyster (Crassostrea virginica). Two EC50 values (effect measured was shell deposition) for this mollusc were 65 µg/l (Butler, 1963) and 380 µg/l (Butler, 1964). Since both tests were conducted at nearly identical salinities (22 °/oo and 21 °/oo, respectively), the increased toxicity shown in the 1963 study may have been the result of the higher test temperature 28°C vs. 19°C in the Butler, 1964 study. Temperature-related toxicity of endosulfan was also reported in rainbow trout by Macek, et al. (1969). The most sensitive species tested was the pink shrimp with a 96-hour LC50 of 0.04 µg/l (Schimmel, et al. 1977).

The acute toxicity of endosulfan to saltwater organisms may be underestimated when LC50 values are based on nominal concentrations, thereby justifying the need to adjust these values for test conditions. For example, Schimmel, et al. (1977) exposed two species of shrimp (Penaeus duorarum and Palaemonetes pugio) and three species of saltwater fishes (Mugil cephalus, Lagodon rhomboides and Leiostomus xanthurus) to endosulfan and reported that all LC50 values based on measured concentrations were lower than those based on nominal concentrations. Variability in species sensitivity of fishes exposed to endosulfan was very small (0.09 to 0.6 µg/l; Table 7) compared with that of invertebrate species tested (0.04 to 380 µg/l). Therefore, use of the greater species sensitivity factor for invertebrate species appears justified. The use of the species sensitivity factor (3.7) applied to fish acute toxicity data seems reasonable and produces a Final Fish Acute Value of 0.061 µg/l. This value is lower than the adjusted LC50 values for all five species tested. Therefore, the sensitivity adjustment factor appears adequate.

For invertebrate species, the use of the species sensitivity factor (49) applied to the geometric mean of invertebrate LC50 values produces a value of 0.044 µg/l (Table 8). Thus, the LC50 values for all but the pink shrimp (six of seven species) are greater than this value (0.044 µg/l; Table 8). According to procedures in the Guidelines, if the LC50 value in a flow-through test (based on measured concentrations) is lower than the geometric mean LC50 value divided by the species sensitivity factor, that LC50 (0.040 µg/l) becomes the Final Invertebrate Acute Value. Obviously, the LC50 for pink shrimp taken as the Final Acute Value is not protective for this species. In fact, Schimmel, et al. (1977) reported that 20 percent of the animals died when exposed to a nominal concentration of 0.01 µg/l endosulfan.

Chronic Toxicity

No data were found in the literature that reported the toxicity of endosulfan to a saltwater fish or invertebrate species over their entire life cycle.

Plant Effects

The only saltwater plant datum available is that of Butler (1963) who reported an 86.6 percent decrease in productivity of natural phytoplankton communities (as measured by 14^C uptake during a 4-hour exposure) when exposed to 1,000 µg/l (Table 9). This level is more than 10,000 times higher than those that produce deleterious effects on fish or invertebrate species in acute studies.

Bioconcentration

Several studies were conducted to determine the bioconcentration of endosulfan by saltwater organisms (Table 10). Roberts (1972 and 1975) investigated the rates of uptake, depuration, and translocation and the bioconcentration factor (BCF) of endosulfan, using the estuarine bivalve *Mytilus edulis*. In both studies, he reported very low BCF values (12 after 112 days to 29 after 14 days); however, no mention was made of the analysis for endosulfan sulfate, the metabolite of technical endosulfan. Analyses for the metabolite are important because Knauf and Schulze (1973) have shown that metabolites of endosulfan that contain the sulphur atom exhibit toxicities to aquatic vertebrates and invertebrates that are similar to those of the technical material. Schimmel, et al. (1977) studied the uptake, depuration and metabolism of endosulfan by the striped mullet. When concentrations of endosulfans I and II and endosulfan sulfate were combined to determine the BCF, Schimmel, et al. (1977) reported an average whole-body BCF of 1,597; nearly all of the endosulfan measured was in the form of the sulfate. Although the uptake portion of the study was conducted for 28 days, the authors question whether a steady- state condition was reached. After two days in an endosulfan- free environment, no endosulfan or sulfate was detectable in the exposed mullet.

Since no maximum permissible tissue concentration is available for endosulfan, no Residue Limited Toxicant Concentration can be generated.

Miscellaneous

No other data from Table 11 suggest any more sensitive effects.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 0.061 µg/l

Final Invertebrate Acute Value = 0.040 µg/l

Final Acute Value = 0.040 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 1,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 1,000 µg/l

0.44 x Final Acute Value = 0.018 µg/l

No saltwater criterion can be derived for endosulfan using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 7. Marine fish acute values for endosulfan

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Striped bass, Morone saxatilis	FT	U	96	0.1	0.077	Korn & Earnest, 1974
Pinfish, Lagodon rhomboides	FT	M	96	0.3	0.3	Schimmel, et al., 1977
Spot, Leiostomus xanthurus	FT	M	96	0.09	0.09	Schimmel, et al. 1977
Spot, Leiostomus xanthurus	FT	U	48	0.6	0.37	Butler, 1964
Striped mullet, Mugil cephalus	FT	M	96	0.38	0.38	Schimmel, et al. 1977
White mullet, Mugil curema	FT	U	48	0.6	0.37	Butler, 1963

* FT = flow-through

**M = measured, U = unmeasured

Geometric mean of adjusted values = 0.226 µg/l $\frac{0.226}{3.7} = 0.061$ µg/l

Lowest value from a flow-through test with measured concentrations = 0.09 µg/l

Table 8. Marine invertebrate acute values for endosulfan

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Eastern oyster, Crassostrea virginica	FT	U	96	65.***	50.***	Butler, 1963
Eastern oyster, Crassostrea virginica	FT	U	96	380.***	293.***	Butler, 1964
Blue crab, Callinectes sapidus	FT	U	48	35.***	11.6***	Butler, 1963
Brown shrimp, Crangon crangon	S	U	48	10.0	3.64	Portman & Wilson, 1971
Korean shrimp, Palaemon macrodactylus	S	U	96	17.1	14.5	Schoettger, 1970
Korean shrimp, Palaemon macrodactylus	FT	U	96	3.4	2.6	Schoettger, 1970
Grass shrimp, Palaemonetes pugio	FT	M	96	1.31	1.31	Schimmel, et al. 1977
Brown shrimp, Penaeus aztecus	FT	U	48	0.4***	0.13***	Butler, 1963
Pink shrimp, Penaeus duorarum	FT	M	96	0.04	0.04	Schimmel, et al. 1977

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* S = static, FT = flow-through

** M = measured, U = unmeasured

***EC50: Abnormal development of oyster larvae; decreased growth of oysters; or loss of equilibrium of shrimp or blue crabs.

Geometric mean of adjusted values = 2.15 µg/l $\frac{2.15}{49}$ = 0.044 µg/l

Lowest value from a flow-through test with measured concentrations = 0.04 µg/l

Table 9. Marine plant effects for endosulfan (Butler, 1963)

Organism	Effect	Concentration (ug/l)
Natural phytoplankton communities	86.6% decrease in productivity; 1,000 ^{14}C in a 4-hour exposure.	1,000

Lowest plant value = 1,000 µg/l

Table 10. Marine residues for endosulfan

Organism	Bioconcentration Factor	Time (days)	Reference
Common mussel, *Mytilus edulis*	12	112	Roberts, 1972
Common mussel, *Mytilus edulis*	29	14	Roberts, 1975
Striped mullet, *Mugil cephalus*	1,597*	28	Schimmel, et al. 1977

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*Bioconcentration factor includes bioconcentration of the metabolite, endosulfan sulfate.

Table 11. Other marine data for endosulfan (Schimmel, et al. 1977)

Organism	Test Duration	Effect	Result (ug/l)
Grass shrimp, *Palaemonetes pugio*	4 days	Bioconcentration factor = 175*	--
Pinfish, *Lagodon rhomboides*	4 days	Bioconcentration factor = 1,173*	--
Spot, *Leiostomus xanthurus*	4 days	Bioconcentration factor = 779*	--
Striped mullet, *Mugil cephalus*	4 days	Bioconcentration factor = 1,115*	--

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*Bioconcentration factor includes bioconcentration of the metabolite, endosulfan sulfate.

ENDOSULFAN

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

Schulze, et al. (1973) presented data from the U.S. Geological Survey program for monitoring pesticides in the streams of the western United States for the period October 1968 to September 1971. At 20 sampling stations, water samples were collected at monthly intervals and analyzed for residues of endosulfan and other pesticides by gas chromatography. No attempt was made to separate suspended sediment from the water for separate analysis. The low detection limit for endosulfan was ~0.005 µg/l. In a total of 546 water samples analyzed, one sample (from the Gila River at Gillespie Dam, Arizona) contained an endosulfan residue of 0.02 µg/l, along with residues of five other organochlorine insecticides.

FMC (1971) reported endosulfan levels in runoff water in North American agricultural areas. Water samples from a pond located in a field treated with endosulfan contained no detectable residues (<10 µg/l). Mud samples from the bottom of the pond, however, contained a maximum of 0.05 mg/kg β-endosulfan and 0.07 mg/kg endosulfan sulfate. These samples were taken approximately 280 days after the last endosulfan application.

In a subsequent study, irrigation runoff was monitored from a field in California treated at a rate of 1.12 kg/ha (FMC, 1972). Water residues (α- and β-endosulfan) were approximately 15 μg/l following the first irrigation but dissipated to below the detection limit (.005 μg/l) after 15 days.

Miles and Harris (1971) measured insecticide residues in the water of a creek flowing into Lake Erie and in ditches draining an agricultural area near Lake Erie. In these water systems, water was sampled weekly and bottom mud was sampled monthly from mid-April to mid-October 1970. No endosulfan residues were found in the creek. In the drainage ditch, endosulfan residues in the water ranged from <2 to 32 ng/l at the pumphouse where the water was lifted into Lake Erie when necessitated by the water level and from <2 to 187 ng/l one mile upstream from the pumphouse. Endosulfan residues in bottom mud were <1 to 1 μg/l (dry weight basis) at the pumphouse, and ranged from 4 to 62 μg/l upstream.

In 1971, in order to compare residue contributions from areas of differing insecticide use, Miles and Harris (1973) determined insecticide residues in water systems draining agricultural, urban-agricultural, and resort areas in Ontario, Canada. Water, bottom mud, and fish samples from these water systems were collected between mid-April and mid- October and analyzed for endosulfan residues by gas-liquid chromatography. Endosulfan residues in individual water samples ranged from <1 to 11 ng/l in Big Creek and from <1 to 3 ng/l in the Thames River (average level for all samples was <1 ng/l); none were found in the Muskoka River (limit of detection 1 ng/l). No endosulfan residues were detected in 18 samples of bottom mud or in a total of 57 fish collected from the three water systems.

The National Research Council of Canada (NRCC) (1975) reports unpublished data (Frank, 1973) on endosulfan residues in water samples collected four times per year between 1968 and 1973 in six southern Ontario rivers and municipal water supplies. Over this period, endosulfan was detected only in one sample, at a level of 0.012 μg/l. In 1973, five water and three sediment sampling sites were monitored at two-week intervals from late March to mid-September, and monthly thereafter. Endosulfan residues were detected only in water during one sampling period at levels of 0.047 to 0.083 μg/l.

Frank, et al. (1977) subsequently published the results of pesticide analysis of 50 sediment samples collected on a grid from Lake St. Clair in 1970 and 1974. In 1970, endosulfan residues were present in the sediments at a mean residue of 0.2 μg/kg (ranging from nondetectable levels (<0.2 μg/kg) to 2.2 μg/kg). Only 20 percent of the samples, however, contained endosulfan and these residues (α- and β-endosulfan with traces of endosulfan sulfate) were confined to sediments from the lower reaches of the ship channel between Lake St. Clair and the Detroit River and offshore from the mouth of the Thames River. Endosulfan was not detected in any of the 1974 samples.

Endosulfan residues in Lakes Erie and Ontario have been reported by the Environmental Quality Coordination Unit (1973) of the Canada Centre for Inland Waters. Of 40 samples of surface and bottom waters from Lake Erie, five contained endosulfan concentrations ranging from 0.005 to 0.014 µg/l. Of 40 Lake Ontario samples, six contained endosulfan at concentrations of 0.005 to 0.051 µg/l. Residues in the sediment samples and in the other water samples were below the detection limits, 0.005 µg/l of water and 5 to 10 µg/kg of sediment.

Wong and Donnelly (1968) measured pesticide concentrations in the St. Lawrence River and in the Bay of Quinte which empties into the northern shore of Lake Ontario. Endosulfan was generally nondetectable in the St. Lawrence River, but a few samples contained endosulfan residues between 0.020 and 0.060 µg/l.

Several laboratories studied the occurrence of endosulfan residues in the Rhine River in West Germany and in the Netherlands following a massive endosulfan-caused fish kill in the Rhine in June 1969 due to an accidental point source contamination. This episode was the result of accidental discharge of approximately 220 lb of endosulfan into the river system rather than from runoff (NRCC, 1975, New York Times, 1969.

Seivers, et al. (1972) monitored the concentrations of endosulfan in the Rhine and Main Rivers in West Germany from June to December 1969. During this period, 55 and 22 water samples were obtained from different locations along the Rhine and Main, respectively. The endosulfan concentrations found in these samples were within the following ranges:

Endosulfan concentration range (ng/l)	Number of samples from	
	Rhine	Main
<100	21 (38%)	3 (14%)
100-500	27 (49%)	1 (4%)
500-1,000	4 (7%)	4 (18%)
1,000-10,000	3 (6%)	9 (41%)
>10,000	0 (0%)	5 (23%)
Total	55 (100%)	22 (100%)

Many communities along the Rhine draw their water supplies from the river. Endosulfan residues in 35 samples of Rhine shore filtrates collected between June, 1969 and February 1970 contained endosulfan concentrations ranging from <10 to 35 ng/l.

Greve and Wit (1971) determined endosulfan concentrations in about 320 samples of surface water and 35 samples of drinking water collected between June 24 and August 31, 1969, from the Dutch section of the Rhine and its tributaries following a massive fish kill the previous June. Endosulfan was identified by gas-liquid chromatography. The maximum concentration of endosulfan ($\alpha + \beta$) found in river water in the Netherlands was 0.70 µg/l on the first day of sampling. From this maximum value, a steady decrease was observed; one month after initiation of sampling, the endosulfan concentration had fallen below the limit of detectability, 0.01 µg/l.

In tests concerning drinking water preparation, Greve and Wit (1971) found that river silt readily adsorbs endosulfan. Of the endosulfan present in raw river water samples, 82 to 85 percent could be removed by filtration or centrifugation. Ferric hydroxide gel and activated carbon were still better adsorbents for endosulfan. Ferric hydroxide gel not only adsorbed endosulfan, but also catalyzed its hydrolysis.

In a more extended monitoring study, Greve (1972) measured endosulfan residues in the Dutch section of the Rhine River from September 1969 to March 1972. During this period, water samples were collected three times a week in the Waal River, the main branch of the Rhine River in the Netherlands. Endosulfan ($\alpha+\beta$) residues were found in 75 percent of the samples, ranging from <0.01 to 0.88 µg/l; the average and median endosulfan concentrations were 0.10 and <0.01 µg/l, respectively, and the upper and lower deciles were <0.01 to 0.29 µg/l.

Wegman and Greve (1978) monitored the Dutch aquatic environment from September 1969 to December 1975 for organochlorine pesticides. Some 1,492 samples were analyzed, including surface water, rainwater, groundwater, and drinking water. The results of these analyses were as follows:

	No. of sample sets analyzed		
Year	Endosulfan[a] containing	Total No.	Maximum endosulfan[a] residue (µg/l)
1969	17	32	0.81
1970	36	45	0.40
1971	9	22	0.25
1972	7	35	0.09
1973	9	22	0.10
1974	1	3	0.02
1975	1	1	0.02

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[a] α- and β-endosulfan; practical detection limit is 0.01 µg/l.

Herzel (1972) monitored organochlorine insecticides in surface waters in the Federal Republic of Germany. Samples of unfiltered water and suspended solids were analyzed from about 25 sites sampled in May 1971, and unfiltered water was analyzed from seven sites sampled monthly between April 1970 and June 1971. All samples were analyzed by gas chromatography, and the detection limits for α- and β-endosulfan were 10 to 30 ng in 30 ml of hexane extract. Of 120 samples of unfiltered surface waters analyzed, eight contained residues of α-endosulfan ranging from 10 to 100 ng/liter, and three contained residues of β-endosulfan ranging from 20 to 95 ng/l. These endosulfan concentrations were found in samples from the Rhine, the lower Main, and the Regnitz and, according to the investigator, originated from industrial effluents.

Of 20 samples of suspended solids, two contained α-endosulfan an at concentrations of 22 and 24 ng, and one contained β-endosulfan at a concentration of 9.6 ng. These values are expressed in terms of the quantities of each endosulfan isomer (in nanograms) found in the solids suspended in one liter of water.

Tarrant and Tatton (1968) studied the presence of organochlorine pesticides in rainwater in the British Isles. The total precipitation collected in each three-month period at seven sampling stations was analyzed by thin-layer and gas-liquid chromatography. The detection limit for endosulfan was about 1 ng/l. No endosulfan residues were detected in any of the 28 composite samples of rainwaters analyzed.

Gorbach, et al. (1971a) investigated the presence and persistence of endosulfan residues in East Java in a river system (Brantas River) and in ponds and seawater following large-scale use of endosulfan on rice in the delta region of the Brantas River. The concentration of endosulfan residues in the water sampled as determined by gas chromatography were as follows:

		Endosulfan residues (µg/l)		
		α	β	Sulfate
Canals	Average	<0.13	<0.12	<0.18
	Range	<0.01-5.8	<0.01-2.4	<0.01-0.55
Fish Ponds	Average	<0.03	<0.02	<0.06
	Range	<0.01-0.25	<0.01-0.08	<0.01-0.44
River system	Average	<0.01	<0.11	<0.19
	Range	<0.01-5.0	<0.01-2.0	<0.01-0.45
Madura Sea	Average	<0.02	<0.02	<0.08
	Range	<0.01-0.09	<0.01-0.07	<0.01-0.28

The highest residue levels (5.8 and 2.4 µg/l of α- and β-endosulfan, respectively) were detected in a canal that drained treated fields shortly after an endosulfan application. Within two days, these high levels decreased to about 0.2 µg/l by degradation and/or dilution with uncontaminated water. Total endosulfan residues (α+ β+ sulfate) averaged 0.46 µg/l.

In connection with the same endosulfan application project in East Java, Gorbach, et al. (1971b) also investigated endosulfan residues in the water and mud of rice fields following an endosulfan treatment. Before treatment of the test fields, total endosulfan residues (endosulfan α+ β+ sulfate) in the water were of the order of 0.5 to 0.8 µg/l as a result of the large-scale endosulfan applications in the area. The test fields were treated by knapsack sprayer at a rate equivalent to about 0.5 lb Active Ingredient (AI)/acre.

After treatment, the initial water concentration of total endosulfan residues in one field was 68 µg/l, declining to the pretreatment value of 0.5 to 0.8 µg/l within five days. In the mud of both submerged test fields, maximum total endosulfan residues were 0.053 and 0.008 mg/kg, respectively, directly after treatment, declining to about 0.01 to 0.02 mg/kg by the fifth day posttreatment. In an adjacent dry rice field, a maximum endosulfan residue of 1.9 mg/kg was found. The sulfate equivalent in the total endosulfan residues increased with time, pointing to conversion of the parent compound in the presence of water.

Several fish kills attributable to endosulfan have been reported from other countries. One major, widely publicized and investigated episode occurred in the Rhine River in West Germany in 1969.

Osmond (1969) reported on an endosulfan-related fish kill which took place in Ontario, Canada, in August of 1969. Analysis of water samples collected where fish had been killed from the Thames River and a tributary where the contamination occurred showed endosulfan concentrations of 0.096 and 0.260 µg/l, respectively. Two other samples taken from upstream on the Thames River and from further up the tributary had endosulfan levels of 0.022 and 0.026 µg/l.

A second fish kill occurred in a pond near Simcoe, Ontario, in 1972 (Frank, 1972). Endosulfan could not be detected in the pond water (limits of detection 0.001, 0.002, and 0.01 µg/l for α-endosulfan, β-endosulfan, and endosulfan sulfate, respectively). However, bottom sediment from one end of the pond contained 0.9, 1.0, and 1.1 µg/kg (dry weight) of α-endosulfan, β-endosulfan, and the sulfate, respectively. Sediment from the other end of the pond contained 1.2 µg/kg (dry weight) endosulfan sulfate.

Ingestion from Foods

Endosulfan is a broad spectrum insecticide and acaricide that is registered in the United States for use in the control of over 100 different insect pests occurring in over 60 food and nonfood crops.

Official U.S. tolerances for pesticide residues in raw agricultural commodities are published in the Code of Federal Regulations, Title No. 40, and in the Federal Register. Appropriate food additive tolerances for processed commodities are published in Title No. 21 of the Code of Federal Regulations. U.S. tolerances for endosulfan and its metabolite are listed in Table 1.

Endosulfan tolerances that have been set by other countries are summarized in Table 2.

The acceptable daily intake (ADI) is defined by Lu (1973) as the daily intake of a pesticide which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at the time of evaluation. It is expressed in milligrams of the chemical per kilogram of body weight (mg/kg).

TABLE 1

U.S. Tolerances for Endosulfan[a]

mg/kg	Crop
0.3	Alfalfa (fresh)
1	Alfalfa hay
0.2[b]	Almonds
1	Almond hulls
2	Apples
2	Apricots
2	Artichokes
0.1[b]	Barley grain
0.2[b]	Barley straw
2	Beans
0.1[b]	Blueberries
2	Broccoli
2	Brussels sprouts
2	Cabbage
0.2	Carrots
0.2	Cattle (meat, fat, meat by-products)
2	Cauliflower
2	Celery
2	Cherries
2	Collards
0.2	Corn, sweet (kernels plus cobs with husks removed)
1	Cottonseed
2	Cucumbers
2	Eggplants
0.2[b]	Filberts
0.2	Goats (meat, fat, meat by-products)
2	Grapes
0.2	Hogs (meat, fat, meat by-products)
0.2	Horses (meat, fat, meat by-products)
2	Kale
2	Lettuce
0.2[b]	Macadamia nuts
2	Melons
0.5[c]	Milk fat
2	Mustard greens
0.2[b]	Mustard seed
2	Nectarines
0.1[b]	Oats, grain
0.2[b]	Oats, straw
2	Peaches
2	Pears
2	Peas (succulent type)
0.2[b]	Pecans
2	Peppers
2	Pineapples
2	Plums
0.2[b]	Potatoes
2	Prunes
2	Pumpkins
0.2[b]	Rape seed
0.1[b]	Rye grain
0.2[b]	Rye straw
0.2[b]	Safflower seed
0.2	Sheep (meat, fat, meat by-products)
2	Spinach
2	Strawberries
0.1[b]	Sugar beets without tops)
0.5	Sugarcane
2	Summer squash
2	Sunflower seeds
0.2	Sweet potatoes
24[d]	Tea, dried
2	Tomatoes
2	Turnip greens
0.2[b]	Walnuts
2	Watercress
0.1[b]	Wheat grain
0.2[b]	Wheat straw
2	Winter squash

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[a] Includes its metabolite, endosulfan sulfate

[b] Negligible residue

[c] Negligible residue in milk

[d] Food additive tolerance

Source: 40 CFR Section 180.182, 1977; 21 CFR Section 193.170, 1977

TABLE 2

Tolerances Reported by Other Countries

Country	Commodity	Tolerances (mg/kg)
Australia[a]	Fat of meat of cattle and sheep	0.2
	Milk and milk products	0.5 (fat basis)
	Fruits, grain, vegetables, cottonseed	1.0
Canada[b]	Peas	0.5
	Artichokes, beans, cauliflower, celery, cucumber, eggplant, grapes, melons, peppers, pumpkins, squash, strawberries, tomatoes, watercress	1.0
	Apples, apricots, broccoli, Brussels sprouts, cabbage, cherries, lettuce, nectarines, peaches, pears, plums, prunes, spinach	2.0
New Zealand[c]	Fruits and vegetables	2.0
Netherlands[c]	Berries, mushrooms	1.0
	Fruit (except berries) and vegetables	0.5
	Potatoes	0.1
South Africa[b]	Cabbage, green beans, boysenberries, youngberries, tomatoes, cucurbits, peas, citrus	2.0
	Peaches, apples, pears	0.5

Source: WHO (1975)

[a] Includes α- and β-endosulfan and endosulfan sulfate

[b] Includes α- and β-endosulfan

[c] Residues not specified

The ADI for pesticides is established jointly by the Food and Agricultural Organization (FAO) Working Party on Pesticide Residues and the World Health Organization (WHO) Expert Committee on Pesticide Residues, and thus is not an officially recognized standard in the United States. The ADI for endosulfan is 0.0075 mg/kg (FAO, 1975).

Corneliussen (1970, 1972) reported the residue levels of several chlorinated insecticides in various foods before and after processing by a dietician. The effect of processing on residues of endosulfan (includes the two isomers and sulfate) are reported for only one food class, leafy vegetables. Corneliussen (1970) reported the residues as 0.011 mg/kg before processing and 0.006 mg/kg after processing. Corneliussen (1972) reported the residues as 0.007 and 0.002 mg/kg, respectively.

McCaskey and Liska (1967) studied the effect of processing on the residues of endosulfan and endosulfan sulfate in milk. One group of milk samples came from cows fed 500 to 2,000 mg/day endosulfan for 7 to 11 days; the other group of milk samples contained endosulfan which had been added in solution in ethyl alcohol. The investigators were not able to detect endosulfan in the milk from the cows fed endosulfan, but the milk did contain endosulfan sulfate. The residues were reported on a milk fat basis since moisture was being removed from the milk during processing. The results are presented below.

	Residue (mg/kg, fat basis)	
Product	Endosulfan sulfate[a]	Endosulfan[b]
Raw milk	15.2	15.9
Forewarmed milk	12.7	12.7
Condensed milk	12.6	11.4
Spray-dried milk	8.8	10.1
Evaporated milk	8.8	9.9
Drum-dried milk	4.5	8.0

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[a] Detected in milk from cows administered endosulfan
[b] Added to milk in alcohol solution

Li, et al. (1970) reported a study in which two dairy cows were given 1 mg/kg/day endosulfan for two weeks. Analyses of the dairy products (pasteurized milk, cream, butter, cheese, dried and condensed whole milk, etc.) indicated only a very small (not quantified) concentration of α-endosulfan. Endosulfan sulfate, however, was not detected.

Johnson, et al. (1975) studied the effects of freeze-drying on the residues of endosulfan in tobacco. The treated samples were analyzed for both endosulfan isomers and endosulfan sulfate. The results are presented in Table 3.

The reduction in endosulfan residues amounted to 34 to 43 percent on a weight basis compared to the control samples. The two types of freeze-drying had about the same effect; the percent reduction in residue was about the same for both high and low initial residue levels. The percent reduction was greater for α-endosulfan than for β-endosulfan or endosulfan sulfate.

TABLE 3

The Effect of Freeze-drying on Endosulfan Residues on Tobacco

Initial pesticide level	Freeze-drying treatment	Residues (mg/kg)[a]			
		α-Endosulfan	β-Endosulfan	Endosulfan sulfate	Total endosulfan
Low	Control	0.12	0.98	2.43	3.53
	Standard Freeze-drying	0.05	0.56	1.59	2.20
	Extraction + freeze-drying	0.05	0.59	1.68	2.32
High	Control	0.25	2.35	7.65	10.24
	Standard Freeze-drying	0.11	1.27	4.45	5.83
	Extraction + freeze-drying	0.10	1.29	4.94	6.33

[a] The analytical method was electron-capture gas chromatography

Source: Adapted from Johnson, et al. (1975)

Beck, et al. (1966) conducted four cattle feeding tests for the purpose of determining residues of endosulfan. In the four tests endosulfan in the tissue, milk, alfalfa, grass, and silage was determined by colorimetric analysis. In one test, the investigators fed alfalfa treated with endosulfan to Hereford steers and analyzed for residues of endosulfan in the omental fat. Two steers were used in each experiment at treatment levels of 0.15, 1.10, 2.50, and 5.00 mg endosulfan per kilogram body weight per day. Two steers (treatment levels 5 mg/kg/day and 2.5 mg/kg/day) developed muscle convulsions (after 2 and 13 days, respectively); the experiments at these levels were discontinued.

After 60 days, one of the steers receiving the 0.15 mg/kg treatment showed no residues of endosulfan in the fat tissue, but one of the steers receiving the 1.10 mg/kg treatment showed 1.0 mg/kg endosulfan in the fat tissue. Two other steers were also fed 1.10 mg/kg of endosulfan in acetone solution twice daily, and after seven days, urine and fecal samples were taken. The two steers excreted endosulfan at the rate of 6.7 and 5.0 mg/day in the feces and 18.5 and 15.9 mg/day in the urine. This rate of excretion accounted for only 7.4 and 4.9 percent of the daily dose administered. Since most of the endosulfan was not excreted or accumulated in the body fat, the investigators concluded that it must have been metabolized.

Beck, et al. (1966) grazed Hereford steers on Coastal Bermuda grass that had been treated with endosulfan. No residues were found in the fat of any of the steers which had been grazing from 31 to 36 days on the treated grass. The levels of endosulfan in the grass varied from 102 mg/kg (dry weight basis) on the first day after treatment (when one test group began grazing) to 1.53 mg/kg on the day the last test group had completed grazing.

Beck, et al. (1966) also fed groups of cows silage made from Coastal Bermuda grass treated with endosulfan. The maximum residue of endosulfan in the silage was 6.43 mg/kg (dry basis), which appeared in the grass treated at 1 lb AI/acre. There were no detectable residues of endosulfan in the milk between the groups of cows which received treated silage and a control group of cows which received untreated silage.

McCaskey and Liska (1967) examined the effect of processing on the residues of endosulfan in milk. The investigators were not able to detect any endosulfan in the milk of cows fed up to 2,000 mg/day for 11 days. However, they did detect 0.6 ppm endosulfan sulfate in a raw milk sample, but the investigators did not state the treatment rate for the cow which produced that sample.

The Food and Drug Administration (FDA), Department of Health, Education and Welfare, monitors pesticide residues in the nation's food supply through two programs. One program, commonly known as the "total diet" or "market basket" program, involves the examination of food ready to be eaten. This investigation measures the amount of pesticide chemicals found in a high consumption varied diet. The samples are collected in retail markets and prepared for consumption before analysis. The other program involves the examination of large numbers of samples obtained when lots are shipped in interstate commerce to determine compliance with tolerances. These analyses are complemented by observations and investigations in the growing areas to determine the actual practices being followed in the use of pesticide chemicals (Duggan, et al. 1971).

A majority of the samples collected in these programs are categorized as "objective" samples. Objective samples are those collected about which there is no suspicion of excessive residues or misuse of the pesticide chemicals. All samples of imported food and fish are categorized as objective samples even though there could be reason to believe excessive residues may be found on successive lots of these food categories.

Market basket samples for the total diet studies are purchased from retail stores, bimonthly, in five regions of the United States. A shopping guide totaling 117 foods for all regions is used, but not all foods are represented in all regions because of differences in regional dietary patterns. The food items are separated into 12 classes of similar foods (e.g., dairy products; meat, fish, and poultry; legume vegetables; and garden fruits) for more reliable analysis and to minimize the dilution factor. Each class in each sample is a "composite". The food items and the proportion of each used in the study were developed in cooperation with the USDA and represent the high consumption level of a 16- to 19-year-old male. Each sample represents a two-week supply of food (Duggan, et al. 1971).

Surveillance samples are generally collected at major harvesting and distribution centers throughout the United States and are examined in 16 FDA district laboratories. Some samples may be collected in the fields immediately prior to harvest. Surveillance samples are not obtained in retail markets. Samples of imported foods are collected as they enter the United States (Duggan, et al. 1971).

The results of these FDA testing programs are intermittently published in Pesticides Monitoring Journal. Pesticide residues are analyzed by multi-residue methods. The residues of endosulfan (total of α- and β-isomers and sulfate) reported in the total diet program are listed in Table 4. The average endosulfan residues in raw agricultural products are listed in Table 5. The average incidence and daily intake of endosulfan based on these data for a six-year period are listed as follows (Duggan and Corneliussen, 1972).

Year[a]/	No. of composites examined	Positive composites (%)	Daily intake (mg)
1965	216	-	-
1966	312	1.6	<0.001
1967	360	0.3	<0.001
1968	360	0.8	<0.001
1969	360	4.2	0.001
1970	360	5.3	0.001

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[a]/ Annual test period is from June of previous year to April of year listed.

TABLE 4

Endosulfan Residues in Total Diet Sample[a]

Class of food	Number of composites containing endosulfan	Amount (mg/kg)	Time period of study and source
Leafy vegetables	1	0.016	June 1965-April 1966 Duggan, et al. (1967)
Garden fruits	3	<0.001, 0.002, and 0.006	
Fruits	1	0.014	
Leafy vegetables	1	0.003	June 1966-April 1967 Martin and Duggan (1968)
Leafy vegetables	1	0.014	June 1967-April 1968 Corneliussen (1969)
Garden fruits	1	0.008	
Oils, fats, and shortening	1	0.0134	
Leafy vegetables	8	<0.001-0.042	June 1968-April 1969 Corneliussen (1970)
Potatoes	2[b]	0.004, 0.011	
Garden fruits	4	<0.001, 0.001, 0.002, 0.007	
Fruits	2	0.002, 0.010	
Leafy vegetables	7	<0.001-0.040	June 1969-April 1970 Corneliussen (1972)
Garden fruits	5	0.001-0.005	
Fruits	3	0.008-0.010	
Oils, fats, and shortening	1	0.185	
Leafy vegetables	15	<0.001-0.063	June 1970-April 1971 Manske and Corneliussen (1974
Potatoes	2	<0.001, 0.007	
Garden fruits	2	<0.001, 0.061	
Fruits	5	<0.001-0.045	
Fruits	6	<0.001-0.006	June 1971-July 1972 Manske and Johnson (1975)
Potatoes	1	<0.001	
Leafy vegetables	7	<0.001-0.008	
Garden fruits	6	<0.001	

TABLE 4 (Continued)

Potatoes	4	<0.001-0.015	August 1972-July 1973
Leafy vegetables	17	<0.001-0.439	Johnson and Manske (1976)
Garden fruits	4	<0.001-0.002	
Fruits	4	<0.001-0.007	
Potatoes	6	<0.001-0.016	August 1973-July 1974
Leafy vegetables	3	<0.001-0.012	Manske and Johnson (1977)
Garden fruits	3	<0.001	
Leafy vegetables	5	<0.001-0.022	August 1974-July 1975
Garden fruits	2	<0.001-0.006	Johnson and Manske (1977)

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[a] Total endosulfan (α-, β-, and sulfate)

[b] Endosulfan sulfate only

TABLE 5

Average Endosulfan[a] Residues in Raw Agricultural Products During 5-year Study (1964-1969)

	Domestic			Imported		
Class of food	No. of samples	Incidence %	Average residue (mg/kg)	No. of samples	Incidence %	Average residue (mg/kg)
Large fruits	6,763	0.8	<0.001	2,495	0.4	<0.001
Small fruits	2,695	2.0	<0.001	496	2.4	<0.001
Leafy and stem vegetables	13,864	4.9	0.01	153	4.0	0.03
Vine and ear vegetables	8,072	1.4	<0.001	1,791	6.7	<0.001

[a] Total includes α- and β-isomer and endosulfan sulfates

Source: Duggan, et al. (1971)

A number of studies have been reported concerning the presence of endosulfan residues in tobacco and tobacco products. The following paragraphs briefly summarize results from these studies.

Dorough and Gibson (1972) reported the residue levels of α- and β-endosulfan and endosulfan sulfate in three brands of cigarettes purchased in the years 1970 to 1972. The residues were determined by gas chromatography; this method has a detection limit of 0.01 mg/kg. In 1970 and 1971 the residues were all below the detection limit. The results for 1972 were as follows:

	Endosulfan residue (mg/kg)			
Brand	α	β	Sulfate	Total
Regular A	0.01	0.12	0.27	0.40
Regular B	0.01	0.14	0.30	0.45
Filter B	0.01	0.10	0.21	0.32
Filter C	0.01	0.09	0.25	0.35
Menthol C	0.01	0.10	0.30	0.41
Average	0.01	0.11	0.26	0.38

Domanski and Sheets (1973) reported the levels of endosulfan residues (total for α- and β-endosulfan plus endosulfan sulfate) in several varieties of 1970 U.S. auction market tobacco. The results are presented in Table 6.

TABLE 6

Endosulfan Residues, U.S. Auction Market Tobacco (1970)

Type	Location	Total endosulfan range	Residue (mg/kg)[a] average
	Tobacco Belt		
Flue-cured	Georgia-Florida	<0.2-11.1	3.6
	North-South Carolina border	0.2-21.9	3.9
	Eastern	<0.2-5.0	1.5
	Middle	<0.2-4.5	1.0
	Old	<0.2-2.7	0.7
	States		
Burley	North Carolina	<0.2-3	0.1
	Tennessee	<0.2	<0.2
	Kentucky	1.4-14.3	8.6
Dark air-cured	Tennessee	0.3-12.5	5.7
	Kentucky	5.8-13.6	8.5
Light air-cured	Maryland	<0.2-3.3	1.5
Dark fire-cured	Tennessee	1.4-4.6	3.2
	Kentucky	2.8-11.9	6.0
	Virginia	0.4-6.5	3.3

[a] Total of α- and β-endosulfan and endosulfan sulfate; the analytical method was electron-capture gas chromatography

Source: Adapted from Domanski and Sheets (1973)

Endosulfan residues on various U.S. tobacco products were reported by Domanski, et al. (1973) for 1971 products and by Domanski, et al. (1974) for 1973 products. Much of the tobacco for the 1971 cigarette samples had been in storage for two or more years. The results are presented in Table 7.

Domanski and Guthrie (1974) reported endosulfan residue levels (total for α- and β-endosulfan plus endosulfan sulfate and several other insecticides) in six brands of cigars purchased in 1972. The residues were determined by gas chromatography. The results for endosulfan were as follows:

Brand	Total endosulfan residues (mg/kg)
1	0.64
2	0.26
3	0.63
4	0.36
5	0.49
6	<0.20
Average	0.41

Gibson, et al. (1974) reported residues of endosulfan in Kentucky Burley tobacco for the years 1963 to 1972. The residues for endosulfan included the two isomers and the sulfate. Endosulfan residues were not detected until 1968. The residues in tobacco from auction warehouses in Kentucky and residues in the Kentucky Burley tobacco pool were as follows:

From auction warehouse in Kentucky		In Kentucky Burley tobacco pool
Year	Residue (mg/kg)	Residue (mg/kg)
1968	0.23	Not reported
1969	0.30	0.86
1970	4.19	2.68
1971	4.60	Not reported
1972	4.10	Not reported

TABLE 7

Endosulfan Residues on U.S. Tobacco Products (1971 and 1973)

Product	Total endosulfan residues (mg/kg)[a] range (average) 1971[b]	Total endosulfan residues (mg/kg)[a] range (average) 1973[c]
Cigarettes	<0.2-0.4 (0.2)	0.36-1.27 (0.83)
Cigars	<0.2-1.1 (0.4)	0.03-1.03 (0.37)
Little cigars	0.3-0.5 (0.4)	0.15-0.26 (0.22)
Smoking or pipe tobacco	<0.2-0.2 (<0.2)	0.08-0.61 (0.37)
Chewing tobacco	<0.2-0.5 (0.2)	0.06-0.86 (0.36)
Snuff	<0.2 (<0.2)	0.06-0.17 (0.12)

[a] The analytical method was electron-capture gas chromatography

[b] Source: Domanski, et al. (1973)

[c] Source: Domanski, et al. (1974)

Thorstenson and Dorough (1976) reported residue levels of α- and β-endosulfan and endosulfan sulfate in "reference" and "alkaloid" cigarettes prepared by the Tobacco and Health Research Institute for the years 1969 and 1974. The "reference" cigarette is a composite which reflects a blend of an "average" domestic unfiltered cigarette; the "alkaloid" cigarettes were composites which contained blends of low-nicotine Burley and flue-cured tobaccos. There were not detectable residues of endosulfan in the 1969 samples. The range and average endosulfan residues in the 1974 samples, which consisted of one alkaloid and three reference cigarettes, were as follows:

	Residue (mg/kg)	
Compound	**Range**	**Average**
α-Endosulfan	0	0
β-Endosulfan	0.4-0.7	0.5
Endosulfan sulfate	0.4-1.1	0.7
Total endosulfan	0.8-1.5	1.2

Schimmel, et al. (1977) reported on both short- and long-term exposures of marine species to endosulfan. Pink shrimp (Penaeus duorarum) did not show any uptake at all when exposed to 0.089 µg/l endosulfan for 96 hours, while grass shrimp (Palaemonetes vulgaris) had 96-hour bioconcentration factors ranging from 164 at 0.40 µg/l (the highest concentration with 0 percent mortality) to 245 at 1.75 µg/l (65 percent mortality). Maximum bioconcentration factors after 96 hours for marine fish were 1,299 for pinfish (Lagodon rhomboides), 895 for spot (Leiostomus xanthurus), and 1,344 for striped mullet (Mugil cephalus). The mullet was also used in a long-term exposure test for 28 days followed by 28 days in clean water. After exposure to 0.035 µg/l endosulfan for 28 days, the bioconcentration factors were 2,429 for edible tissue and 2,755 for whole body. After two days in clean water, endosulfan was not detected (limits of detection = 0.01 µg/g in tissues). The investigators noted that in all exposure tests endosulfan sulfate was the predominant and often sole form of endosulfan found in the tissues.

Roberts (1972) studied the accumulation of endosulfan in common mussels (*Mytilus edulis*) when exposed to levels of 0.1, 0.5, and 1.0 mg/l endosulfan in seawater. The concentration factors determined from these tests were as follows:

Endosulfan concentrations (mg/l)	Exposure period (days)							
	14	27	42	56	70	85	100	112
	Bioconcentration factors							
0.1	13.0	17.0	13.5	19.3	22.5	16.1	17.0	17.0
0.5	4.7	5.8	4.9	8.3	6.9	7.0	7.8	11.0
1.0	2.8	3.3	3.7	3.9	6.5	7.4	7.1	8.1

Roberts (1972) also reported a rapid fall in tissue residue levels (1 to 2 mg/kg for all three exposure levels) within 58 days of removal from endosulfan-containing waters.

In further studies, Roberts (1975) investigated the differential uptake of endosulfan by tissue of *M. edulis*. Eighty mussels approximately 60 mm (2.4 in.) in length were exposed to 0.1 mg endosulfan per liter in slowly flowing seawater for 36 days, then transferred to clean seawater for a further period of 23 days. Weekly samples of six mussels were taken for determination of endosulfan residues in the digestive gland, the mantle plus gonad, the gills, and the remaining tissue, consisting of pedal retractor muscles, foot, and anterior and posterior adductor muscles.

Results showed that the major site of concentration of endosulfan is the digestive gland. The approximate maximum endosulfan residues found and the times at which they occurred (in number of days after initial exposure) were as follows, expressed as micrograms endosulfan (both isomers) per gram of wet weight:

Digestive gland	6.1 after 7 days
Mantle and gonad	1.8 after 36 days
Gills	2.1 after 15 days
Remaining tissue	2.3 after 36 days
Mean residue level	2.5 after 36 days

Upon removal of the mussels to clean seawater, the endosulfan residue levels initially declined fairly rapidly in all tissues; the greatest decline occurred in the digestive gland during the first 14 days of elution. During the final six days of elution, the rate of residue loss was similar for all tissues.

Ernst (1977) also evaluated the bioconcentration of endosulfan in M. edulis in static tests. The inital concentration of endosulfan was 2.05 µg/l, and it reached a steady state concentration of 0.14 µg/l. The concentration factor for -endosulfan calculated from the tissue levels of the steady state concentration in the water was 600. The half-life for elimination of the residue was calculated to be 33.8 hours.

Roberts (1975) also conducted endosulfan uptake studies with the scallop (Chlamys opercularis). In this species, endosulfan concentrations in the digestive gland and in the foot, and anterior and posterior adductor muscles were similar to those seen in M. edulis. However, the endosulfan level in the gills of M. edulis was almost five times that in gills of C. opercularis, while the reverse was true in the gonad and mantle tissues. The mean tissue residue levels for both species, estimated from the summated values for the separate tissues, were very similar despite the differences in distribution between tissues.

Gorbach (1972) referred to an experiment in which goldfish (Carassius auratus) were exposed for five days to 1 µg/l ^{14}C-labeled endosulfan in water. The fish attained endosulfan concentrations of 0.4 µg/g or a bioconcentration factor of 400. It was also stated that the parent compound as well as all metabolites were excreted within 14 days when the fish were transferred to fresh water.

Oeser, et al. (1971) held goldfish for five days in a test solution containing mean residues of 350 µg/l ^{14}C-labeled endosulfan. The average ratio of body residues to skin residues of 205:1 indicated that most of the endosulfan was in the fish body, not the skin. After 14 days in fresh water, the test fish had excreted 96 percent of the radioactivity that had been absorbed in the test solution.

Investigations by Schoettger (1970) with ^{14}C-labeled endosulfan indicated the compound is taken up and deposited in various tissues of fish at varying rates. The liver and gut (with feces) contained the most pesticide whereas the heart, blood, gill, kidney, and brain showed slower uptake rates; less was found in gut (empty), skin, and muscle. The investigator noted that in general those tissues containing relatively large amounts of blood contained the higher concentrations of residues, with the exception of the gut and feces. Radiotracer and chemical analysis techniques showed a water-soluble metabolite of endosulfan in the bile of western white suckers (*Catostomus commersoni*), northern creek chubs (*Semotilus atromaculatus*), and goldfish. Schoettger (1970) suggests that endosulfan degrades to its alcohol, which is then conjugated with glucuronic acid and excreted with the feces.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 12 was obtained for endosulfan using the common mussel which probably contains about one percent lipids (Roberts, 1972). A later study produced a BCF of 29 in only 14 days (Roberts, 1975). The BCF is much higher if the metabolite endosulfan sulfate is included (Schimmel, et al. 1977). For the purpose here a BCF of 12 will be used. An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the common mussel to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for endosulfan and the edible portion of all aquatic organisms consumed by Americans is calculated to be 12 x 2.3 = 28.

Inhalation

According to the American Conference of Governmental Industrial Hygienists (ACGIH, 1977), the Threshold Limit Value-Time Weighted Average (TLV-TWA) for endosulfan is 0.1 mg/m^3. The tentative value for the Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) is 0.3 mg/m^3. The TLV-TWA is based on a normal eight-hour workday or 40-hour workweek, day-after-day exposure. The TLV-STEL is the maximum concentration to which a worker may be exposed continuously for as long as 15 min without irritation, chronic or irreversible tissue changes, or narcosis sufficient to increase the inclination to accident or to affect self-rescue or work efficiency. Up to four such exposures may occur per day provided at least 60 min elapse between the exposures and provided the TLV-TWA is not exceeded in the time lapses.

Apparently neither Occupational Safety and Health Administration (OSHA) exposure limits nor National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits have been established for endosulfan (NIOSH, 1978a). Further, a recent international comparison of hygienic standards for chemicals in the work environment did not list standards for endosulfan (Winell, 1975).

Lee (1976) summarized the results of intensive ambient air sampling at selected locations over the nation in which samples were analyzed for pesticide residues. Samples were collected during 1970, 1971, and 1972. The results of these tests for endosulfan-containing samples are given in Table 8.

Wolfe, et al. (1972) evaluated potential respiratory exposure for a number of pesticides. Tests were conducted by sampling spraymen operating tractor-drawn power air-blast equipment as they applied pesticides to fruit orchards. Endosulfan was applied as a 0.08 percent spray. The estimated respiratory exposure was 0.01 to 0.05 mg/hour (average 0.02 mg/hour).

Exposure to endosulfan was found by respirator pad analysis to be greater during mixing operations than in spraying operations. With a five-min exposure time, 182,800 ng of endosulfan were detected on the respirator pad during a mixing operation; only 4,664 ng were detected during a 30-min spraying operation (Oudbier, et al. 1974).

TABLE 8

Summary of Endosulfan Residues in Air Samples from 16 States

		1970					1971				
				Concentration (mg/m^3)					Concentration (mg/m^3)		
State	Residue name	No. of samples	Positive samples (%)	Arithmetic mean	Mean of positive samples	Maximum value	No. of samples	Positive samples (%)	Arithmetic mean	Mean of positive samples	Maximum value
Arkansas	α-Endosulfan	72	6.94	1.1	15.5	27.1	60	ND	ND	ND	ND
	β-Endosulfan		11.11	2.4	22.0	54.5		ND	ND	ND	ND
Illinois	α-Endosulfan	53	7.55	2.2	28.8	39.5	36	ND	ND	ND	ND
Kansas	α-Endosulfan	64	12.50	5.5	43.8	70.7	49	ND	ND	ND	ND
Kentucky	α-Endosulfan	68	32.35	159.4	492.8	2,256.5	43	ND	ND	ND	ND
Montana	α-Endosulfan	48	16.67	13.9	83.5	211.7	36	ND	ND	ND	ND
North Carolina	α-Endosulfan	54	9.26	0.7	7.2	10.9	41	ND	ND	ND	ND
All 16 states	α-Endosulfan	-	6.61	13.0	111.9	2,256.5	-	ND	ND	ND	ND
	β-Endosulfan		1.02	0.2	22.0	54.5		ND	ND	ND	ND

		1972				
				Concentration (mg/m^3)		
Arkansas	α-Endosulfan	64	ND	ND	ND	ND
	β-Endosulfan		ND	ND	ND	ND
Illinois	α-Endosulfan	59	ND	ND	ND	ND
Kansas	α-Endosulfan	65	ND	ND	ND	ND
Kentucky	α-Endosulfan	66	ND	ND	ND	ND
Montana	α-Endosulfan	69	ND	ND	ND	ND
North Carolina	α-Endosulfan	64	ND	ND	ND	ND
All 16 states	α-Endosulfan	-	ND	ND	ND	ND
	β-Endosulfan		ND	ND	ND	ND

Tessari and Spencer (1971) analyzed air samples from human environments for pesticide residues. Nylon screens were placed inside and outside the homes of 12 men occupationally exposed to pesticides, including endosulfan, for a period of one year, five days each month. Endosulfan residues were found in 13 of 52 indoor air samples from the formulators' households. In the positive samples, endosulfan residues ranged from 0.22 to 4.52 µg/m^2 of filter; the mean of the positive samples was 1.77 µg/m^2. The positive samples came from only two households, and the householders in both cases were formulators who had handled endosulfan. No endosulfan residues were found in the outdoor air near any of the formulators' households, or in the indoor or outdoor air at the farmers' households.

NRCC (1975) reported unpublished data (Boelens and Frank, 1973) on endosulfan spray drift from an aerial spray application of endosulfan to a tobacco field in Norfold County, Ontario, Canada (endosulfan formulation and rate of application not given in secondary source.). Residues in various parts of the field were determined based on levels detected in pans filled with water. Endosulfan levels detected in the water within the field were 55.0 mg/l between tobacco rows; 8.5 mg/l under plants in the rows; 20.0 mg/l in an opening in the field; and 0.01 mg/l at the edges of the field. No detectable (detection limit not reported) endosulfan residues were found at the edge of the field at the soil surface. Water in an adjacent stream contained endosulfan residues ranging from traces to 0.22 mg/l. Sediment from the stream contained 2.7 mg/kg of endosulfan in a sample collected opposite the field's drainage and 0.23 and 0.37 mg/kg in two other samples collected nearby. Aquatic monocotyledonous plants contained 0.01 mg/kg.

Keil, et al. (1972) observed endosulfan spray drift in a field test on tobacco in South Carolina. Three treatments of endosulfan (formulation and AI content not given) at the rate of 0.5 lb AI/acre per treatment were applied by ground equipment to single-row (12-ft) plots separated by guard rows. Each treatment or control plot was replicated four times in a completely randomized design. Samples of tobacco foliage were collected for residue analysis at 11 posttreatment intervals ranging from one day after the first application to 18 days after the third.

Even though the experimental design included guard rows, endosulfan residues ranging from 0.037 to 0.679 mg/kg resulting from spray drift were found on plots treated with another insecticide, and on untreated control plots. However, in most instances (18 to 22 samples from plots not treated with endosulfan), the residue from drift was less than the least significant difference at the 95 percent probability level, 0.363 mg/kg endosulfan.

Dermal

The 1977 listing of TLV values showed a "skin" designation for endosulfan (ACGIH, 1977). This designation refers to the potential contribution to the overall exposure by the cutaneous route including mucous membranes and eyes, either by airborne endosulfan or by direct contact with it.

Wolfe, et al. (1972) also evaluated potential dermal exposure of spraymen applying a 0.08 percent endosulfan spray. The estimated dermal exposure was 0.6 to 95.3 mg/hour (average 24.7 mg/hour).

Possible intoxication due to the dermal exposure was suggested by Kazen, et al. (1974) who analyzed hexane hand rinsings and found that endosulfan persisted on exposed workers' hands for 1 to 112 days after exposure.

PHARMACOKINETICS

Absorption

Undiluted endosulfan is slowly and incompletely absorbed in the mammalian gastrointestinal tract (Maier-Bode, 1968). However, when endosulfan is dissolved in a carrier vehicle such as cottonseed oil, the oil and the insecticide are readily, though not completely, absorbed by rats (Boyd and Dobos, 1969) and other mammals (Maier-Bode, 1968). The β-isomer is more readily absorbed than the α-isomer (Demeter, et al. 1977).

Alcohols, oils, and emulsifiers also accelerate the absorption of endosulfan by the skin (Maier-Bode, 1968).

Inhalation is not considered to be an important route of uptake of endosulfan because of its low vapor pressure (9×10^{-3} mm Hg) (Maier-Bode, 1968).

When endosulfan is dissolved in chloroform and painted on the shaven skin of rabbits, it is readily absorbed (Gupta and Chandra, 1975).

A 1:1,000 dilution of endosulfan instilled on the conjunctiva of rabbit's eyes caused neither pain nor subsequent inflammation, which was apparently because of rapid removal by the lacrimal fluid (Hoechst, 1967a).

Distribution

After ingestion, endosulfan is first distributed to the liver and then to the following organs: brain, heart, kidneys, lungs, spleen, testes, thymus gland, suprarenal glands, mammary glands, skeletal muscles, and the remainder of the gastrointestinal tract (Boyd and Dobos, 1969; Maier-Bode, 1968).

Two reports of individuals committing suicide by ingesting endosulfan present some data regarding the distribution of endosulfan in man. Demeter, et al. (1977) report on one victim who ingested a preparation containing 12.4 percent α- and 8.1 percent β-endosulfan. The order of distribution was as follows: stomach contents > small intestine contents > liver > kidneys > urine > blood.

The following table summarizes the data reported by Coutselinis, et al. (1978) from three suicide cases.

TABLE 9

Concentration Levels of Endosulfan in Biological Material

Case	Blood (mg/100 ml)	Liver (mg/100 g)	Kidney (mg/100 g)	Brain (mg/100 g)
1	0.4	0.08	0.24	0.025
2	0.8	0.1	0.32	0.03
3	0.7	0.14	0.28	0.028

Source: Coutselinis, et al. (1978)

Metabolism and Excretion

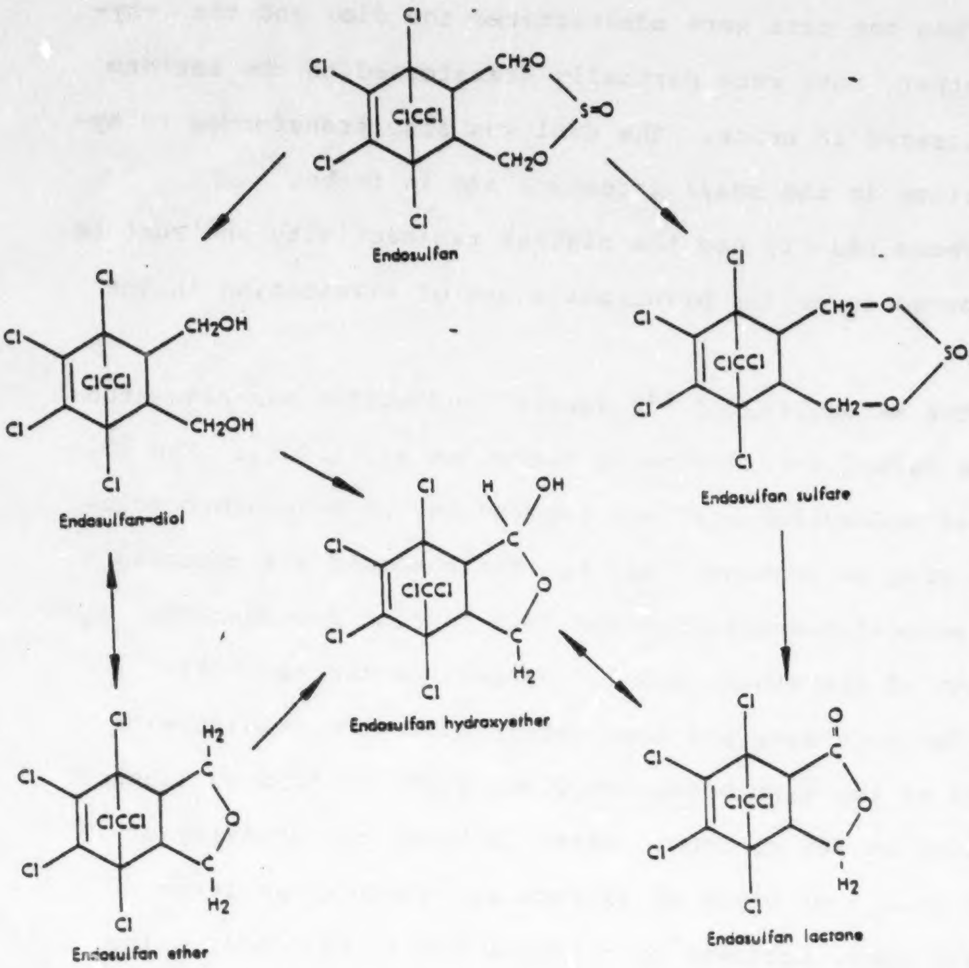
The metabolism of endosulfan in mammalian species has been widely investigated. The generalized metabolic pathway for endosulfan in animals is given in Figure 1.

Demeter and Heyndrickx (1978) have detected endosulfan sulfate as a metabolite in humans by analysis of two human postmortem cases. Both were male, and both had taken a 20 percent endosulfan product by mouth within hours of death, in one case under three hours. Endosulfan sulfate was not detectable in blood or urine but was present in liver (3.4 mg/kg average), brain (0.5 mg/kg), and kidney tissue (0.4 mg/kg).

No other information was found regarding the metabolism of endosulfan (or endosulfan sulfate) in humans.

In a review by Matsumura (1975) a pathway for metabolism in rats, mice, and insects was presented which differed somewhat from that given by Knowles shown in Figure 1. Matsumura did not show the transformation of the ether to the hydroxyether but indicated the hydroxyether was formed directly from either the diol or the lactone (Matsumura, 1975).

The results of a study using 14C-labeled endosulfan indicated the sulfate to be the metabolite most commonly present in organs, tissues, and feces of rats whether dosed with the α- or β-isomer (Whitacre, 1970). The feces also contained large amounts of unchanged endosulfan. Endosulfan diol, α-hydroxyether, and lactone were recovered from both urine and feces of rats fed either endosulfan isomer.


Endosulfan
Endosulfan-diol
Endosulfan sulfate
Endosulfan hydroxyether
Endosulfan ether
Endosulfan lactone

Source: Knowles (1974), Menzie (1974)

Figure 1. Metabolism of endosulfan in animals

When the rats were administered the diol and the -hydroxyether, both were partially transformed to the lactone and excreted in urine. The diol was also transformed to hydroxyether in the small intestine and in feces.

Feces usually had the highest radioactivity and must be considered to be the principal route of elimination in the rat.

The metabolism of ^{14}C-labeled endosulfan was also studied in BALB/C strain mice by Deema, et al. (1966). The ^{14}C-labeled endosulfan used was labeled in the hexachlorocyclodiene ring at carbons 5 and 6. The compound was composed of 58.3 percent α-endosulfan and 35.6 percent β-endosulfan, 6.0 percent of the ether, and 1.0 percent of the alcohol.

Two male mice and four female mice were studied with groups of two each being fed 0.30, 0.25, or 0.20 mg labeled compound in 300 mg food. After 24 hours the activity of label in 1 g of organ or excreta was greatest in feces (98,452 cpm), followed by visceral fat (7,053 cpm), urine (3,746 cpm), liver (2,883 cpm), kidney (1,390 cpm), brain (424 cpm), respired CO_2 (302 cpm), and blood (92 cpm). Total recovery of the labeled endosulfan was approximately 65 percent.

Purified unlabeled endosulfan was also fed at 0.3 mg/mouse in a 300 mg food pellet. After 24 hours large amounts of endosulfan sulfate were found in the liver, small intestine, and visceral fat with a trace in skeletal muscle and kidney. The endosulfan was found only in the stomach, small intestine, and feces. By chromatography, a metabolite that appeared to be identical with endosulfan alcohol was detected in urine.

When mice were fed only the α-isomer of endosulfan, the material was detected in the stomach, small intestine and feces although endosulfan sulfate was detected in the liver, small intestine, visceral fat and feces. Endosulfan alcohol was found in urine. Neither the parent compound nor any of its metabolites were detected in the brain.

When the β-isomer was fed, endosulfan sulfate was found in the liver, kidney, small intestine, muscle, and visceral fat. The alcohol was detected in the urine, but neither the β-isomer nor any metabolites were detected in the brain.

When ten mice were fed diets containing 10 mg/kg purified endosulfan for 28 days, endosulfan sulfate was detected in the liver and visceral fat of all animals although lower amounts were detected than in organs of other test mice 24 hours after they had been fed a single 0.3 mg dose. Endosulfan isomers or metabolic products were not detected in the brain, but a product having the same retention time as endosulfan alcohol was detected in the urine. When the feces were analyzed, both isomers, endosulfan sulfate, endosulfan alcohol and endosulfan ether were detected.

Endosulfan alcohol was detected in the urine of animals fed either endosulfan sulfate, endosulfan ether or endosulfan diol.

The principal metabolic products produced in the mouse under the conditions of this study were endosulfan sulfate and endosulfan alcohol (Deema, et al. 1966).

Dogs (unspecified breed or number of each sex) were administered α- and β-endosulfan for 28 days at 0.35 and 1.75 mg/kg/day (FMC, 1963). Upon analysis only traces of α- and β-endosulfan were detected in the urine (0.02 to 0.1 ppm), but large amounts (13 to 25 percent of the endosulfan fed) were detected in the feces.

In a study with two East Frisian milk sheep, radiolabeled endosulfan (65 percent α and 35 percent β) that was administered as a single oral dose of 0.3 mg/kg was almost entirely eliminated in 22 days (Gorbach, et al. 1968). About 50 percent of the radiolabel was excreted in the feces, 41 percent in the urine, and one percent in the milk. On the 22nd day the level in the milk was 2 µg/l.

The highest blood concentrations of radiolabel were reached after 24 hours (4.3 to 4.5 x 10^{-4} percent of administered activity).

The maximum elimination in feces was observed on the second day (20.8 and 18.6 percent of administered dose). The unchanged isomers were detected in the feces; the lactone, diol, and hydroxyether of endosulfan were not detected in the feces.

Radioactivity peaked in urine in the first 24 hours (18.5 percent of the dose) and then decreased. Two metabolites were detected in urine, one characteristic of endosulfan alcohol and the other characteristic of the hydroxyether. Of the activity, 70 percent was present in the alcohol and 30 percent in the hydroxyether.

After 40 days the organ with the highest concentration of radiolabel (0.03 μg/g) was the liver.

The investigators noted that no fat-soluble metabolite other than endosulfan sulfate was detected in the milk of the test animals and that no major metabolite was retained in fat or in the organs for long periods of time (Gorbach, et al. 1968).

In another study, between 0.1 and 0.2 mg/l endosulfan sulfate was detected in the milk of cows that had been given 2.5 mg/kg α-endosulfan, 2.5 mg/kg β-endosulfan, and 5 mg/kg endosulfan sulfate in the feed for 30 days (FMC, 1965). Less than 0.005 mg/liter endosulfan sulfate was detected in the milk 20 days after administration of the insecticide was stopped.

The half-life of endosulfan in the milk of cows that survived poisoning was reported to be 3.9 days (Braun and Lobb, 1976). These residues were present primarily as endosulfan sulfate. The endosulfan isomers were detectable in milk for six days in one animal and 13 days in another, with a detection limit of 0.001 mg/l. Endosulfan sulfate residues were detected for 35 days in both animals. Blood contained detectable amounts of the sulfate metabolite (0.025 mg/l) for one day after exposure. Parent isomers were not found in blood.

In sheep given single oral doses of ^{14}C-labeled endosulfan at 14 mg/kg, the half-life of radiolabeled endosulfan in the feces and urine of sheep was reported to be about two days (Kloss, et al. 1966).

Dorough, et al. (1978) studied the fate of endosulfan in female rats given the insecticide by esophageal intubation. Five days after a single radiolabeled dose, 88 percent of the α-isomer and 87 percent of the β-isomer were recovered in the urine (13 percent) and the feces (75 percent). Two days after a single dose was given to rats with cannulated bile ducts, 47 percent of the α-isomer and 29 percent of the β-isomer were secreted in bile.

After another group of these rats had eaten diets containing endosulfan for 14 days, the half-life of the residues was determined to be approximately seven days.

The last group of rats was fed 5 mg/kg endosulfan metabolites (the sulfate, diol, -hydroxyether, lactone, and ether derivatives) for 14 days. The organs containing the greatest amounts of endosulfan derivatives were the kidneys (1 µg/g) and the liver (3 µg/g).

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Values for the LD_{50} of technical endosulfan (an ∼2:1 mixture of α- and β-endosulfan) via oral, intraperitoneal, and dermal routes are shown in Table 10. The oral LD_{50} for technical endosulfan for rats ranged from 18 to 121 mg/kg, and varied with the technical material or formulation used,

TABLE 10

Acute Toxicity of Endosulfan

Test animal (sex) (strain)	Endosulfan or formulation	Solvent (carrier)	Number of animals per test group	Route of administration	LD_{50} (mg AI/kg)[a]	Source
Rat (-) (Sprague-Dawley)	Purified	Corn oil	-	Oral	40-50	Lindquist and Dahm (1957)
Rat, M (Sherman)	Technical	Peanut oil	60 total	Oral	43 (41-40)	Gaines (1969)
Rat, F (Sherman)	Technical	Peanut oil	70 total	Oral	18 (15-21)	Gaines (1969)
Rat (-) (-)	Technical	-	-	Oral	35	Jones et al. (1968)
Rat, M (Wistar)	Technical	-	-	Oral	121 (± 16)	Boyd and Dobos (1969)
Rat (-) (-)	α-endosulfan	-	-	Oral	76 mg/kg	Hoechst (1967b)
Rat (-) (-)	β-endosulfan	-	-	Oral	240 mg/kg	Hoechst (1967b)
Rat, M (-)	Technical	Alcohol	16/treatment group	Intraperitoneal	46.7 (36.4-51.8)	Gupta (1976)
Rat, M (-)	Technical	10% alcohol in peanut oil	16/treatment group	Intraperitoneal	89.4 (73-107.4)	Gupta (1976)
Rat, F (-)	Technical	Alcohol	16/treatment group	Intraperitoneal	22.1 (18.6-26.9)	Gupta (1976)
Rat, F (-)	Technical	10% alcohol in peanut oil	16/treatment group	Intraperitoneal	48.6 (36.4-51.8)	Gupta (1976)
Rat (-) (-)	HOE 2671 (20% AI)	Alcohol	6/treatment group	Intraperitoneal	8 (6.1-10.1)	Lendle (1956)
Rat (-) (-)	HOE 2671 (sol. powder)	Alcohol	4/treatment group	Intraperitoneal	13.5 (9.5-19.3)	Lendle (1956)
Rat, M (Sherman)	Technical	Xylene	60 total	Dermal	130 (104-163)	Gaines (1969)
Rat, F (Sherman)	Technical	Xylene	70 total	Dermal	74 (58-94)	Gaines (1969)
Rat, M (-)	Thiodan®	-	-	Inhalation, 4 hours	350 mg/m³	Ely et al. (1967)
Mouse, M (-)	Technical	Alcohol	16/treatment group	Intraperitoneal	6.9 (5.4-8.9)	Gupta (1976)
Mouse, M (-)	Technical	10% alcohol in peanut oil	16/treatment group	Intraperitoneal	12.6 (9.4-16.8)	Gupta (1976)
Mouse, F (-)	Technical	Alcohol	16/treatment group	Intraperitoneal	7.5 (5.3-10.1)	Gupta (1976)
Mouse, F (-)	Technical	10% alcohol in peanut oil	16/treatment group	Intraperitoneal	13.5 (10.6-16.8)	Gupta (1976)
Rabbit, F (Albino)	Technical (90%)	Chloroform	4/treatment group	Dermal	182 (± 36)	Gupta and Chandra (1975)
Rabbit, F (Albino)	Technical (> 91%)	Chloroform	4/treatment group	Dermal	167 (± 21)	Gupta and Chandra (1975)

[a] AI - Active ingredient.

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the kind of vehicle used for administration, and the sex of the animal. These data indicate that endosulfan by oral, intraperitoneal, or dermal route is more toxic to female rats than to males regardless of the kind of vehicle used for administration (ACGIH, 1971).

Some difference in toxicity occurs whenever different vehicles are used as the carrier. Lendle (1956) quoted an LD_{50} of only 8 mg/kg when endosulfan was dissolved in ethyl or isopropyl alcohol and given intraperitoneally to rats, but similar animals treated with endosulfan in cottonseed oil have an LD_{50} as high as 48.6 mg/kg.

In another study (Gupta, 1976), male rats given endosulfan in alcohol exhibited an LD_{50} at 46.7 mg/kg, but similar males given the material in ten percent alcohol in peanut oil exhibited an LD_{50} at 89.4 mg/kg. While the amount of endosulfan necessary to yield an LD_{50} was less for female rats, the twofold difference between administration in the two different vehicles remained the same.

Boyd and Dobos (1969) estimated the largest nonlethal dose (LD_o) to be 60 mg/kg and the smallest totally lethal dose of endosulfan (LD_{100}) to be 180 mg/kg in Wistar rats.

Truhaut, et al. (1974) demonstrated that there were differences in the toxicities of endosulfan to different rodents: the LD_{50} of 96 percent pure endosulfan administered orally to rats and hamsters was 64 ± 4 mg/kg in the rat and 118 ± 16 mg/kg in the hamster. The maximum dose without fatality was 40 mg/kg for the rat and 70 mg/kg for the hamster. Biochemical measurements, or effects of endosulfan dosing on enzyme levels, showed that in the hamster, endosulfan inhibited cholinesterase significantly, whereas there was no effect on rat cholinesterase. On the other hand, the activities of enzymes GPT and LDH were significantly elevated by endosulfan dosage in the rat, but in the hamster they were unaffected.

The difficulty in extrapolating LD_{50} data from one animal to another was demonstrated in a study by Li, et al. (1970), who estimated (based on rat data) that 12.5 mg/kg would be an acceptable dose for (Brown-Swiss and Holstein) dairy cattle. Within ten hours of dosing, however, the two treated cows were in an extreme state of excitation, and six days after dosing one of the animals (Brown-Swiss) died.

The effects of accidental dermal exposures of cattle to endosulfan were reported by Thompson (1966). Two hundred and fifty cattle (breed, age, and sex not reported) were accidently sprayed with a five percent endosulfan miscible oil concentrate diluted 1 to 300, giving a wash concentration of approximately 0.12 percent endosulfan. The cattle were sprayed early in the morning. Signs of toxicity were noted in 50 of the 250 animals by about noon. Four cattle were dead by 4 p.m. and six more died by the next morning. The symptoms of exposure were those of hyperexcitability (Thompson, 1966).

An accidental poisoning of three cows with endosulfan was reported, which occurred when the animals ate grass which had been sprayed with an endosulfan emulsion spray (reported as 35 percent endosulfan) ten months before. Analysis of the organs of one of the animals with gas chromatography showed the presence of α-endosulfan at 7 to 9 μg/kg, β-endosulfan at 3.5 to 4.5 μg/kg, and metabolites as high as 9 mg/kg (Schmidlin-Meszaros and Romann, 1971).

Four of five crossbred male and female calves, weighing 60 to 170 kg, died within 24 hours after being dusted with a four percent dust formulation of endosulfan. Symptoms of toxicity included frenzied activity, violent convulsions, blepharospasm, and overall extreme hyperexcitability. One of the animals was necropsied, and no gross lesions were seen. Laboratory analysis revealed 0.73, 3.78, and 0.10 mg/kg endosulfan in the brain, liver, and rumen contents, respectively (Nicholson and Cooper, 1977). This report indicates excellent skin absorption in cattle, and probably a toxic dosage much lower than that reported for rats, for which 110 mg/kg is an experimental fatal dose (Dreisbach, 1974). Milk and tissue were also analyzed from another dairy herd which was exposed to endosulfan; 9 of 18 animals exposed died (Braun and Lobb, 1976). Liver, kidney, and muscle tissue contained endosulfan sulfate at a level of 4.2, 1.1, and 0.6 mg/kg, respectively. Milk from one of the survivors contained 1 μg/kg endosulfan sulfate at the end of five weeks, at the time a blood sample contained 0.025 mg/kg endosulfan. The symptoms of exposure were like those described in the first report.

The signs of toxicity observed in rabbits were similar to those in rats and mice, the onset occurring three to six hours after exposure. Hyperexcitability, dyspnea, decreased respiration, discharge from the eyes, and tremors were followed by convulsions. The convulsions appeared at intermittent or regular intervals. The animals preferred to rest on the sternum with the forelimbs extended. Eventually the animals lost response to painful stimuli. This loss first occurred in the hindlimbs and then spread to the forelimbs followed by loss of motility, loss of corneal reflex, a deep coma, and death (Gupta and Chandra, 1975).

In cattle dermally exposed to endosulfan the signs of toxicity consisted of listlessness, blind staggers, restlessness, hyperexcitability, muscular spasms, goose-stepping, and violent "fits" (Thompson, 1966).

Three other reports of accidental animal poisoning (species not specified) describe the toxic effects of endosulfan exposure (Panetsos and Kilikidis, 1973; Utklev and Westbye, 1971; Schmidlin-Meszaros and Romann, 1971, all cited by Demeter and Heyndrickx, 1978). The effects reflected an induced neurotoxicity and were roughly analogous to those in endosulfan-poisoned humans.

A survey by California veterinarians reported on the occurrence of domestic animal poisoning by organochlorines, including the death of calves following contamination of feed bunks with endosulfan. No specific instances or dose levels were reported, but signs of poisoning and treatment were tabulated (Maddy and Riddle, 1977). Signs of poisoning included apprehension, hypersensitivity and spasms of the eyelids and front quarters progressing to the hind quarters; these spasms may be continuous or intermittent. Clonic-tonic seizures, loss of coordination, circling frontward or backward, and abnormal posturing is seen. The animal may become comatose. The veterinary treatment emphasizes agents to control particularly violent neuromuscular activity in severe poisonings (Maddy and Riddle, 1977).

Ely, et al. (1967) report that the inhalation four-hour LC_{50} of endosulfan was 0.35 mg/l for male rats. Under similar test conditions the four-hour LC_{50} for female rats was 0.08 mg/l. Whether these values are from work done by Ely, et al. or are quoted from some other report, however, is not clear. Details on procedures, numbers of animals, etc., were not given.

Gupta and Chandra (1975) studied the eye irritation properties of endosulfan. When aqueous suspensions of 5, 10, and 20 percent endosulfan were instilled into one eye each of six rabbits (two per group) no irritation or congestion was observed in any of the animals.

A 1:1,000 endosulfan dilution instilled in rabbit eyes caused neither pain nor subsequent inflammation (Hoechst, 1967a).

Skin irritation and skin sensitization studies have apparently not been made with endosulfan, although one report notes that the skin of rabbits treated dermally with endosulfan at 100 mg/kg did not exhibit any cutaneous abnormalities (Gupta and Chandra, 1975).

Signs of poisoning in dogs dosed orally with 200 and 500 mg/kg body weight were increased saliva formation, vomiting, and tonic and clonic cramps (Hazleton Laboratories, 1967). Signs of toxicity in endosulfan-exposed cattle have been described earlier in this section.

Gross necropsy of rats fed endosulfan at near the LD_{50} range (see Table 10) revealed congestion of the brain and an acute gastroenteritis. Dark reddish areas were often seen in the kidneys, liver, spleen, and thymus. The skin was of normal appearance. Edema of the interstitial tissue of the testes was noted.

A loss of organ weight was observed in most animals, but significantly so in cardiac stomach, kidneys, liver, skin, spleen, testes, and thymus (Boyd and Dobos, 1969).

Gupta and Chandra (1975) report that following an acute dermal exposure of rabbits to endosulfan at 100 mg/kg of body weight, necropsy revealed congestion in the kidneys, peritoneum, and the muscles underlying the skin. No other gross pathological conditions were observed. Microscopic examination of the liver revealed marked congestion and dilation of sinusoids. In some of the lobules hepatocytes were observed undergoing degenerative changes around central veins. Sections of the kidneys from treated animals showed groups of glomeruli with shrunken tufts and thickened Bowman's capsules. Occasionally the epithelium of the proximal convoluted tubules were necrotic and desquamated. The adrenals of treated animals exhibited cell disruption, foamy cytoplasm, and eccentric nuclei in the zona reticularis.

Necropsy of cattle that died following an accidental (dermal) exposure to endosulfan did not reveal any great pathological changes, although congestion and edema of the lungs along with froth in the trachea were observed (Thompson, 1966).

The liver was the principal target, with increased weight and an apparent increase in drug metabolizing enzymes (Gupta and Gupta, 1977a, 1977b). Rats that were dosed on either 7 or 15 consecutive days with 2.5 or 5.0 mg/kg technical endosulfan showed liver effects. Neither testes nor adrenals of the endosulfan-treated animals differed in weight from the controls.

The kidney, stomach, and intestine of fish were adversely affected by exposure to a 35 percent emulsifiable concentrate formulation of endosulfan at levels of 0.4 and 0.8 µg/l, and the same dose also severely damaged the liver (Amminikutty and Rege, 1977; 1978). Acute treatment involved observation of histological change that occurred in fish 96 hours after the formulation was added to the fish water. The 96 hour LC_{50} was 1.6 µg/l, and renal tubular cells were affected. Both stomach and intestinal mucosa were severely damaged. Fish, chronically exposed to levels of 0.4 and 0.53 µg/l for 16 weeks showed hyperplasia of the kidney and necrosis of intestinal mucosa cells (Amminikutty and Rege, 1978). The same dose levels and time produced vacuolated and ruptured hepatic cells, as well as frequent total destruction of pancreatic islet cells (Amminikutty and Rege, 1977).

A toxic effect unreported in other studies, testicular atrophy in male Osborne-Mendel rats, was seen in the recent carcinogenicity bioassay (Weisburger, et al. 1978). Testicular pathology occurred in 18/47 (38 percent) of the group receiving 445 mg/kg endosulfan of 98.8 percent purity in the diet, and in 24/47 (51 percent) of the group receiving 952 mg/kg. The pathology was characterized by degeneration and necrosis of the germinal cells lining the seminiferous tubules. Three of 19, or 16 percent of the control rats had testicular atrophy in this study. Male mice of the B6C3F1 strain, receiving 6.9 and 3.5 mg/kg in the diet, in the same study, showed a slight indication of testicular atrophy with pathology in 3 of 50 high dose and 2 of 50 low dose. Control mice had neither testicular inflammation nor atrophy.

Protein-deficient male Wistar strain rats were reported to be four times as susceptible to the toxic effect of technical grade endosulfan as rats having adequate protein nutrition. The toxicity of the pesticide was determined after the rats had been fed for 28 days on a purified diet low in protein. Test animals were compared to rats on the purified diet with normal protein and to rats on standard laboratory chow.

With the purified diet containing no additional protein the LD_{50} in rats was 5.1 ± 1.4 mg/kg. At dietary protein levels of 3.5, 9.0, 26.0, and 81 percent (28 days' feeding) endosulfan LD_{50}'s in rats were 24 ± 10, 57 ± 4.0, 102 ± 16, and 98 ± 7 mg/kg, respectively. The LD_{50} value for endosulfan when given in standard laboratory chow was 121 ± 16 mg/kg (Boyd and Dobos, 1969; Boyd, et al. 1970).

Toxicity of endosulfan sulfate to mammals is about the same as the parent compound. However, the endosulfan alcohol, hydroxyether, and lactone have LD_{50}'s ranging from 150 to 1,500 mg/kg in the rat (Gorbach, 1972).

Dorough, et al. (1978) determined the acute oral toxicities of endosulfan and its apolar metabolites to female albino mice. The approximation method used results in values that correlated very closely with LD $_{50}$values. The most toxic compounds were endosulfan sulfate (8 mg/kg), -endosulfan (11 mg/kg), and -endosulfan (36 mg/kg). With these compounds, no symptoms of poisoning were seen until the lethal dose was almost reached, and the lethal doses caused convulsions and death within one hour. Four other metabolites were tested: Endosulfan -hydroxyether, endosulfan lactone, endosulfan ether, and endosulfandiol, with acute lethal doses of 120, 120, 270, and over 2,000 mg/kg, respectively. For ease of comparison, these values are tabulated:

Approximate Lethal Dose of Endosulfan and Apolar Analogs to Mice

Compound	Dose (mg/kg)
α-endosulfan	11
β-endosulfan	36
Endosulfan sulfate	8
Endosulfan -hydroxy ether	120
Endosulfan lactone	120
Endosulfan ether	270
Endosulfandiol	>2,000

Source: Adapted from Dorough, et al. (1978)

Rats were reported to tolerate endosulfan at oral doses of up to 3.2 mg/kg/day for three months without observed injury (Czech, 1958).

The no-effect level for dogs was considered to be 30 mg/kg feed (~0.75 mg/kg/day) (FMC, 1967).

A no-effect level for endosulfan in rats was studied with respect to induction of microsomal liver enzymes (Den

Tonkelaar and Van Esch, 1974). The activities of aniline hydroxylase, aminopyrine demethylase, and hexobarbital oxidase in experimental groups each consisting of six Wistar male rats were compared with those of six control animals. Results from aniline hydroxylase induction studies indicated that when endosulfan was fed in the diet at 200 mg/kg for two weeks the activity of the enzyme was 123 percent of the control (statistically greater); at 50 mg/kg the activity of the enzyme in treated animals was nearly the same as the control (slightly less). Treatment with endosulfan at a dietary level of 200 mg/kg also statistically increased the activity of aminopyrine demethylase but not the activity of hexobarbital oxidase. The no-effect dietary level for endosulfan for rats was considered to be 50 mg/kg.

A six-week toxicity study, dosing 98.8 percent pure endosulfan in the diet, was performed at five dose levels on B6C3F1 mice, five males and five females per dose, and a similar number of Osborne-Mendel rats (Weisburger, et al. 1978). Concentrations of endosulfan in the rat group were 178, 316, 562, 1,000 and 1,780 mg/kg, and in the mouse groups 3.2, 5.6, 10, 18, and 32 mg/kg. Animals were dosed six weeks, then observed two more weeks while on regular diet. A control group for each species received the vehicle and normal lab chow.

In male rats, a nine percent depression in mean body weight occurred at 562 mg/kg, and a 20 percent depression at 1,000 mg/kg. No depression in body weight as a function of dose occurred in female rats. In both sexes of mice, depression in mean body weight was observed at concentrations of 5.6 mg/kg and above.

Deaths and the endosulfan dose levels:

Rats: 3/5 males, 1,780 mg/kg
1/5 females, 316 mg/kg
4/5 females, 562 mg/kg
Mice: 1/5 males, 10 mg/kg
1/5 females, 5.6 mg/kg

Weight gain of young female rats fed either 5 or 50 mg/kg endosulfan in the diet for 15 days was used as an indicator of the compound's effect on animals exposed to the insecticide subacutely. Both groups gained weight at the control rate, and there was no difference in the weight of livers or kidneys of endosulfan-exposed rats when compared to control (Dorough, et al. 1978).

The compounds used in this test were purified - and - endosulfan added as an acetone solution to ground animal feed. Feed was checked by extraction and chromatography when freshly prepared and after remaining in the feeding cup 24 hours. The four feeding groups were:

13 rats, α-endosulfan isomer-5 mg/kg
13 rats, β-endosulfan isomer-5 mg/kg
4 rats, α-endosulfan isomer-25 mg/kg
4 rats, 7:3 mixture of α:β-endosulfan-25 mg/kg

Dogs were reported to "tolerate" endosulfan at doses up to 0.75 mg/kg for one year (Hazleton Laboratories, 1959a).

Oral doses of about 10 and 100 mg/kg endosulfan in the diet were administered to rats for two years (Hazleton Laboratories, 1959b). Low survival of females and reduced testis weight in males were seen at the low dose. Consistent histopathological findings were apparent at the high dose level, which produced renal tubular damage and some hydropic change of the liver.

Synergism and/or Antagonism

The two human fatalities reported by Demeter and Heyndrickx (1978) both involve endosulfan ingested with alcohol (although dimethoate was also in one formulation). The authors suggest that synergism between alcohol and endosulfan is likely and they reference the statements of Lendle (1956) who demonstrated an increased gastrointestinal absorption of endosulfan in the presence of alcohols.

The acute toxicity of a diethylphosphorothioate (bromophos-ethyl) was examined when dosed with endosulfan for synergistic effects. A group of ten rats was orally dosed with 1/2 LD_{50} of endosulfan, or 24 mg/kg, at the same time they received 1/2 LD_{50} of bromophos-ethyl. The mortality expected was 5/10 or 50 percent; 6/10 died within the one week observation period, which indicates no synergistic activity occurred (Muacevic, 1973).

Endosulfan was reported by Gupta and Gupta (1977a) to decrease the pentobarbital-induced sleeping time in endosulfan-treated rats. Animals receiving the two higher doses of endosulfan showed significant increases in time to sleep induction and shortening of the sleeping time. Although the blood and brain concentrations of pentobarbital were significantly reduced at 30 min (reflecting the reduced response observed), there were no differences in concentrations of pentobarbital in blood and brain in control and treated animals when the rats awoke. This indicated to the authors that the inhibitory effect on pentobarbital by endosulfan is not due to a change in the sensitivity of the brain, but could be due to enhanced metabolism of pentobarbital.

The influence of endosulfan on rat hepatic drug metabolizing enzymes and lipid peroxidation was also measured to define how endosulfan modifies the action and metabolism of other compounds by affecting the mixed function oxidase system (Agarwal, et al. 1978). A marked increase in the activity of aminopyrine-N-demethylase, aniline hydroxylase and tyrosine amino-transferase was found, as well as an increase in spontaneous lipid peroxidation. The increases were all dose dependent at the levels of 2.5 and 5.0 mg/kg (Agarwal, et al. 1978). The increase of the demethylase as well as the hydroxylase enzyme suggests that endosulfan is a nonspecific inducer of drug metabolism.

Teratogenicity

Technical grade endosulfan was tested for teratogenic and embryotoxic effects in rats by Gupta, et al. (1978). The insecticide was suspended in corn oil and given orally from day six through day 14 of gestation in doses of 0.0, 5.0, and 10.0 mg/kg. On day 21 of gestation, both dams and fetuses were examined for pathology. There was a significant increase in fetal mortality and resorption sites in endosulfan-treated rats: control rats had 5.5 percent resorption without any dead fetuses, whereas endosulfan-treated rats had 20 to 22.8 percent resorptions. No malformations of any significance were noted in 463 fetuses from 59 dams. The authors conclude that the study demonstrated no teratogenic effect, but that the administration of endosulfan to pregnant rats produced a dose related increase in maternal toxicity, which they attributed to a possible effect on the female sex hormones (Gupta, et al. 1978).

Pure endosulfan was tested for embryotoxicity in the fertile eggs of White Leghorn chickens at levels of 10 to 500 mg/kg. Injections were made to the center of the yolk using corn oil or acetone as the carrier. At 100 mg/kg, endosulfan in acetone reduced hatchability by 54 percent compared to controls; 100 mg/kg endosulfan in corn oil reduced hatchability by 24 percent compared to controls (Dunachie and Fletcher, 1969). Endosulfan at 500 mg/kg in acetone showed 53 percent hatchability compared to controls.

In similar studies, Smith, et al. (1970) evaluated the embryotoxic effects of endosulfan on chickens. When 72 eggs per treatment and six treatment levels were studied (0.07 to 1.5 mg/egg yolk injection) hatchability was reduced from the zero control level of 80.0 to 77.3 percent at 1.5 mg/egg. At the lowest concentration tested percent hatchability was not affected (Smith, et al. 1970).

In other tests 5 mg endosulfan per egg reduced hatchability to 60 percent (Dunachie and Fletcher, 1966).

Lutz and Lutz-Ostertag (1972) conducted a study in which eggs from hens of mixed breeding (Rhode Island Red-Wyandotte White and Rhode Island Red-Wyandotte White--Light Sussex crosses) were dipped into or sprayed with endosulfan in alcohol or acetone solutions at concentrations from 0.5 to 5 percent. Following treatment the eggs were incubated normally. Gonads from male and female chick embryos at days eight and nine of incubation were explanted on agar medium to which three drops of a 0.5 to 1.0 g/l solution of endosulfan were added.

These investigators reported that the spray and dip treatments of the eggs resulted in alterations in the gonads of the embryos in both males and females. The cultured gonads underwent hypertrophy and became vacuolized; thus, there was a tendency to sterility of the gonads.

Lutz-Ostertag and Kantelip (1970; 1971) performed similar experiments on quail eggs (*Coturnix coturnix japonica*). They concluded that endosulfan had no teratogenic effect on the quail at the doses employed, but the male and female embryos were sterilized, and, according to the authors, was due to the antimitotic toxicity exhibited by endosulfan.

Mutagenicity

Endosulfan, of unreported concentration, purity, and other detail, was positive as a base-pair substitution mutagen in direct Salmonella tests (without microsomal activation). The microbiological tests employed the *Salmonella typhimurium* histidine auxotrophs TA1535, TA1536, TA1537, and TA1538 (Adams, 1978).

Neither isomer of endosulfan, nor metabolites endosulfan ether and endosulfan sulfate were active in the Salmonella mutagenicity test with or without the S-9 liver homogenate. Metabolites endosulfan diol, α-hydroxyether and the lactone severely inhibited bacterial growth even at 10 μg per plate, so the Ames test on these compounds produced inconclusive results (Dorough, et al. 1978). All compounds were screened using the four *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1978 following dose response tests at 10, 100, 500, and 1,000 ug per plate, and were compared to a positive control, 2-acetylaminofluorene.

Endosulfan gave negative results when tested for mutagenicity in *Saccharomyces cerevisiae* (mitotic gene conversion at the ade two and trp five loci), *Escherichia coli* (forward mutation to streptomycin resistance at the str A gene locus), and *Serratia marcescens* strains a 21 and a 742 (back mutation to prototrophy). Test dose levels were not given (Fahrig, 1974).

The most relevant tests for predicting risk to humans are positive results from *in vivo* mammalian tests which assess the chemical's tendency to produce germ cell mutations. The heritable translocation test in rodents is probably the best test to show chromosomal rearrangements, although the difficult and expensive specific locus test in inbred mice is also satisfactory.

For assessing risk to man on the mutagenicity of endosulfan, data that are necessary also includes the demonstration that the proposed mutagenic metabolite actually can reach the germ cells of mammals when the compound is dosed. Further, knowledge of the comparative metabolism of endosulfan in the test species versus that of man is needed.

No tests have been run which define mammalian suppression of DNA repair, disturbed segregation of chromosomes, or outright production of gene mutations or chromosomal aberrations.

Studies have been conducted that include Ames tests on endosulfan isomers and proposed metabolites using four common *Salmonella typhimurium* strains and liver homogenate S-9 fraction. No mutagenicity was seen in defined systems, although three of five metabolites were toxic to the bacteria.

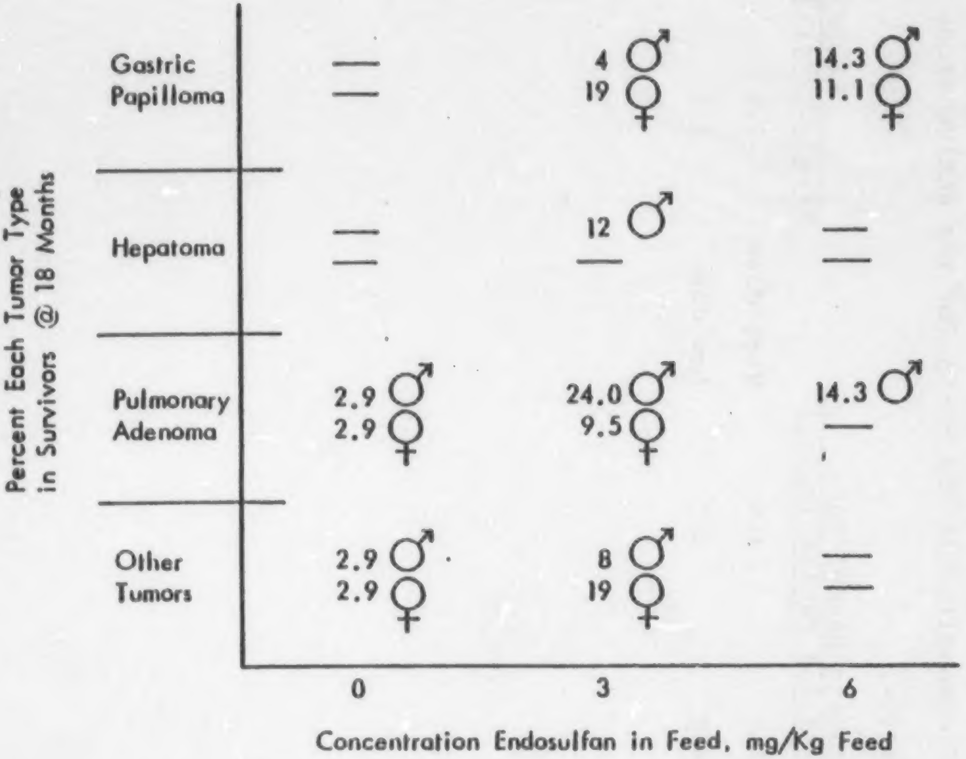
Carcinogenicity

Two bioassay tests by the NCI have been run on endosulfan. In the first test (Kotin, et al. 1968; Innes, et al. 1969) a 96 percent pure mixture of the isomers of endosulfan was administered to mice by two routes: either as an injection in dimethylsulfoxide (DMSO) on the 28th day of age (2.15 mg/kg, subcutaneously) or by stomach tube orally on days 7 to 28 (2.15 mg/kg in gelatin) following which the compound was mixed with ground feed at levels of 3 and 6 mg/kg feed.

The mice, C57Bl/6 and C3H/AnfF1 strains of both sexes, showed incidences of tumors during the nearly 18 months of feeding as tabulated (see Figure 2). Innes, et al. (1969) summarized the statistical analyses and concluded there was no evidence of endosulfan carcinogenicity.

In the second NCI bioassay on endosulfan, technical grade endosulfan of 98.8 percent purity was dissolved in corn oil and mixed with the feed for 50 Osborne-Mendel rats of each sex and 50 B6C3F1 mice of each sex. Chemical administration was for 78 weeks after which rats were observed for 33 additional weeks and mice for 14 additional weeks. The trials on male rats were terminated early, week 82 for high dose and week 74 for low dose. Time-weighted average concentrations of endosulfan in the diets for the entire study are tabulated below.

	Osborne-Mendel Rats			B6C3F1 Mice	
	Male (mg/kg)	Female (mg/kg)		Male (mg/kg)	Female (mg/kg
High dose	952	445	High dose	6.9	3.9
Low dose	408	223	Low dose	3.5	2.0



Percent Each Tumor Type in Survivors @ 18 Months

	0	3	6
Gastric Papilloma	— ♂ — ♀	4 ♂ 19 ♀	14.3 ♂ 11.1 ♀
Hepatoma	— —	12 ♂ —	— —
Pulmonary Adenoma	2.9 ♂ 2.9 ♀	24.0 ♂ 9.5 ♀	14.3 ♂ —
Other Tumors	2.9 ♂ 2.9 ♀	8 ♂ 19 ♀	— —

Concentration Endosulfan in Feed, mg/Kg Feed

Figure 2. Tabulation of mouse tumor data from NCI bioassay on endosulfan (Kotin, et al. 1968)

The doses of endosulfan used in these studies were toxic to the kidney of rats of both sexes and to male mice. Male rats also had testicular atrophy, and high early death rates occurred in both species of male mice. Due to these early deaths, the bioassay was not conclusive with regard to males, but enough females survived to conclude that technical grade endosulfan is not a carcinogen to female B6C3F1 mice or to female Osborne-Mendel rats.

The official NCI summary recommended against retest of endosulfan based on the early male animal mortality, since in the female test animals, the chemical was noncarcinogenic.

Interesting relationships that were not discussed in the official summaries appear when the data are examined closely. Table 11, which presents tumors by site and ignores the early deaths, shows that there were move liver and lung tumors in the male mice than in matched controls, but this increased occurrence of tumors is not dose-dependent: there were 6/49 liver tumors in the low dose males but only 2/50 in the high dose, and 1/20 in the matched controls. Again, in the occurrence of alveolar/bronchiolar carcinoma, the matched controls had 0/20, but both high and low dose male mice had two in populations of 50 and 49, respectively.

Early mortality occurred in the males of both rats and mice, but was a particular problem in the rats. A generalized toxic nephropathy probably contributed most significantly to the early deaths, but signs commonly associated with aging in group-housed laboratory rats were reported in equal numbers in both dosed and control animals during the last 6 months. The table below summarizes the early mortality. In necropsies of the early deaths, several lesions were found, but no actual dose-response pattern was evident, so no cause was ascribed by the authors to the early animal deaths. The most prevalent lesions include: nephropathy, parathyroid hyperplasia, and testicular atrophy in male rats. Cannibalism was the most common cause of early death in male mice.

ANIMAL SURVIVAL TIMES: TUMOR BIOASSAY STUDIES

Species	Sex	Dose level or control	% living at study end (110 wk=rats 90 wk=mice)
Rat	Male	High	0[a]
		Low	0[b]
		Control	25
	Female	High	50
		Low	62
		Control	70
Mice	Male	High	10
		Low	39
		Control	15
	Female	High	96
		Low	94
		Control	85

[a] 15% alive @ wk 74; ended trial 36 wk early

[b] 20% alive @ wk 82; ended trial 28 wk early

TABLE 11

Target Organs for Endosulfan-Induced Tumors $\frac{\text{incidence}}{\text{population}}$

			Lung	Lymphomas/ Leukemias	Kidney	Liver	Endocrine	All other sit
Osborne-Mendel rats	Male	High dose[a]	0/47	1/47	2/47	0/47	0/47	0/47
		Low dose[b]	0/50	2/50	3/50	0/50	1/50	4/50
		Controls	1/20	4/20	2/20	0/20	7/20	0/20
	Female	High dose[c]	1/50	1/50	3/50	1/50	11/50	15/50
		Low dose[d]	1/50	3/50	2/50	1/50	19/50	27/50
		Controls	0/20	1/20	1/20	0/20	13/20	14/20
	Male	High dose[e]	2/50	0/50	0/50	2/50	0/50	6/50
		Low dose[f]	2/49	0/49	0/49	6/49	0/45	1/49
		Controls	0/20	0/20	0/20	1/20	0/20	3/20
B6C3F1 mice	Female	High dose[g]	0/50	6/50	0/50	1/50	1/50	3/50
		Low dose[h]	6/50	10/50	0/50	0/50	0/50	4/50
		Controls	2/20	6/20	0/20	0/20	0/20	1/20

Summarized from NCI Bioassay Data (Weisburger, et al. 1978)

[a] 952 mg/kg feed

[b] 408 mg/kg feed

[c] 445 mg/kg feed

[d] 223 mg/kg feed

[e] 6.9 mg/kg feed

[f] 3.5 mg/kg feed

[g] 3.9 mg/kg feed

[h] 2.0 mg/kg feed

The 95 percent confidence intervals on the relative risk of developing a tumor furnish additional insight into the statistical implications of these data. Many of the confidence intervals, due to the early mortality, have an upper limit greater than one, indicating the theoretical possibility that the test did not conclusively address the possibility of tumor induction by endosulfan. In all cases except one, however, the relative risk is unrelated to the dose of endosulfan received. The occurrence of fibrosarcoma of subcutaneous tissue in male mice showed a relative risk greater than one when compared to both pooled controls and with matched controls, and the risk was dose-related (Table 11, NCI Bioassay, Weisburger, et al. 1978). The high incidence of fibrosarcoma of subcutaneous tissue in all control male mice suggests this difference is unimportant to the overall carcinogenicity of endosulfan.

Figure 3 illustrates time to tumor data for rats and mice for this study.

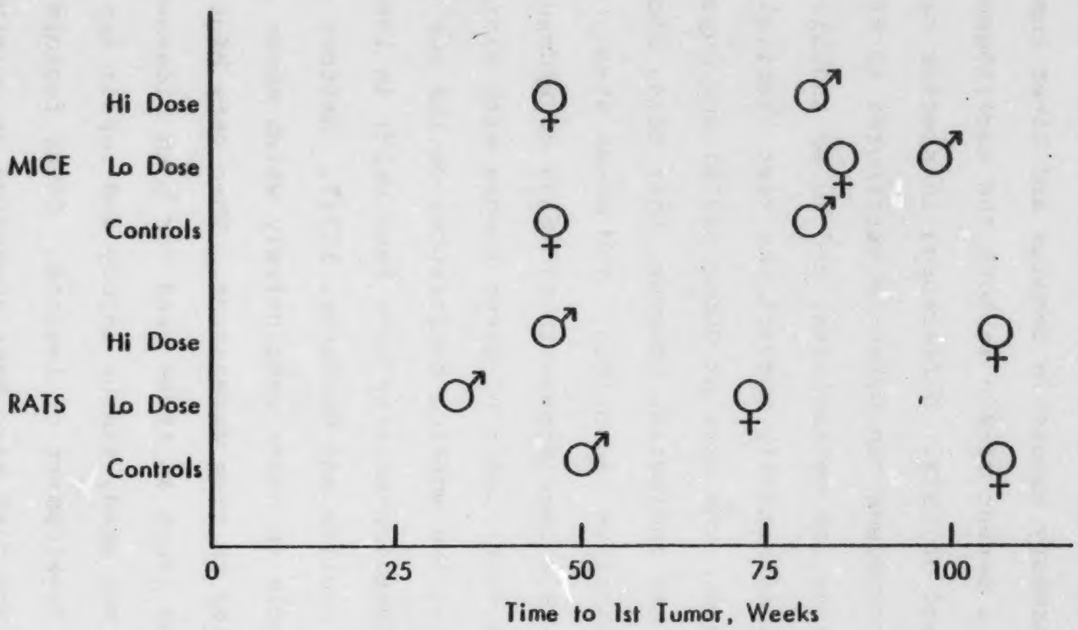


Figure 3. Scattergram of time to tumor, rat/mouse endosulfan bioassay.

Source: Tabulated from NCI bioassay data (Weisburger, et al. 1978).

The significance of the negative carcinogenicity data in the latest NCI bioassay is increased by several factors involved in the choice of model, which was a stringent test for carcinogenicity.

The C3H strain of mouse has one of the highest known incidences of mammary tumors in females and liver tumors in males, and was a parent strain in both the carcinogenesis bioassay of 1968 and of 1978. Differences in species responses to chemical carcinogens can often be attributed to differing metabolic pathways and metabolites, and to an inability of some species to effectively convert the test chemical to an active carcinogen. The work of Gupta (1978) and Gupta and Chandra (1975) has indicated, however, that rats, mice, and rabbits all metabolize endosulfan. The mouse strain used by the NCI in the 1978 carcinogenesis bioassay of endosulfan is so prone to the development of liver tumors with minimal stimulation, that two working conferences on the use of such mice to assess carcinogenicity have been held; in 1969 (IARC, 1971) and 1975 (Butler and Newberne, 1975). Neither conference has been able to state conclusively which mouse data should be applied to risk assessment. When very high levels of test compound (such as those used for both bioassay trials of endosulfan) are used, tissue injury and repair may be important in the development of lesions. Other factors such as sex, hormones, and diet have been suggested as possible modifiers of the carcinogenic activities of primary carcinogens. The distinct differences in toxicity to males versus females seen in many endosulfan tests makes it quite likely that hormonal differences influenced the final test result in the carcinogenicity bioassays.

The Osborne-Mendel rat, also used in the NCI bioassay of endosulfan (Weisburger, et al. 1978), is known to be a strain very resistant to toxicity, so that high dose levels for extended periods can be administered. This increases the likelihood for survival and the appearance of any tumors that would be missed in trials with early deaths (Tomatis, et al. 1973). The fact that toxicity and early deaths occurred in the male Osborne-Mendel rats in the 1978 endosulfan bioassays is another indication that doses were more than adequate to produce an effect if the chance existed to produce one.

These animal models give an additionally severe test of carcinogenicity in that the parent mice of these inbred strains carry tumor viruses. In the 1968 NCI bioassay, for example, the AKR strain has a high rate of leukemia by six to eight months of age. Use of the C3H strain, with the murine mammary virus, and the AKR strains of mice means these bioassays are also testing for promotion mechanisms of the test chemical. There are no known human tumors that occur by promotion of a human tumor virus, so the use of these strains to test for carcinogenicity is a severe trial. In addition, Henschler (1977) has suggested that mice in general have a particularly low activity of epoxide hydrase, i.e., mice have a decreased ability compared to other animals to detoxify reactive epoxides, which are the reactive and toxic intermediates formed in vivo as metabolites in many industrial chemicals.

Route of exposure, used in the NCI trials (high dietary levels), is less relevant to human exposure (dermal and inhalation of particulates) than it is to domestic animals. While these bioassay trials did not measure gastrointestinal absorption, it is likely that a high concentration of endosulfan reached the liver by the portal circulation with each meal taken by the test rodents. Endosulfan that reaches the liver complexing and detoxification mechanisms by dermal or inhalation routes do so after passage through tissue, the blood stream, and contact with many cellular mechanisms. The oral route is a particularly severe test for liver effects, and the lack of such effects in these trials is further indication of a clean bill of health for the carcinogenicity of endosulfan. It is also worthy of note that absorption from the gastrointestinal tract is the route that is most likely to ensure that metabolites of endosulfan as well as the alpha and beta isomers impinge upon not only the liver but also other organs and tissues of the body.

Ely, et al. (1967) reported that one or more convulsions occurred in each of nine workers exposed to a 50 percent endosulfan wettable powder. Six of the nine cases were known not to have had a history of previous convulsions, but the previous history of the other three was uncertain. A causal relationship between convulsions and exposure to endosulfan was, however, considered highly likely.

The potential vulnerability of the central nervous systems of humans to endosulfan was demonstrated in epileptic convulsions and altered EEG patterns in three subjects exposed to the pesticide. In one of the patients, occasional EEG alterations were observed one year after the exposure (Tiberin, et al. 1970).

Five human deaths due to endosulfan were reported by Terziev, et al. (1974), two of which were accidental poisonings and three of which were the result of intentional intake. Details were lacking, but the most significant postmortem findings as described by Terziev were circulatory disorders, protein dystrophy in the parenchymal organs, acute lung emphysema, and severe changes in the neurons.

Two poisoning cases resulting in human fatalities were reported with 20 percent endosulfan products, and both involved interaction with other chemicals (alcohol in one case and alcohol with dimethoate in the second). Demeter and Heyndrickx (1978) found α- and β-endosulfan in the different tissues of the victims as follows:

Organ/Tissue	Endosulfan Levels
Small intestine	314 and 289 mg/kg
Blood	Below 0.1 and 0.075 mg/l
Brain	4.1 mg/kg and unreported
Kidney	11.4 and 4.28 mg/kg
Urine	Below 0.1 and 2.65 mg/l

Alcohol was present in the blood and urine of both poisoning fatalities at a level of 2.34 and 1.81 mg/l for blood and 3.46 and 2.47 mg/l for urine. One of the men was extremely nauseous when found, and died shortly afterward. The other was found dead, with an extremely cyanotic appearance. No other symptoms of toxicity were reported.

The intentional ingestion of unknown quantities of a 35 percent emulsifiable concentrate formulation of endosulfan resulted in three human fatalities. Coutselinis, et al. (1978) analyzed blood and viscera and reported that the average concentration levels of both isomers of endosulfan were 0.63 mg/ 100 ml blood; 0.11 mg/100 g liver tissue; 0.28 mg/100 g kidney tissue; and 0.028/100 g brain.

Seven European countries that have heavy use of endosulfan were queried for user reports of toxicity or allergic manifestations in normal usage. No symptoms that might be connected with the normal application of endosulfan have become known with regard to humans (Hoechst, 1966).

Israeli, et al. (1969) report three cases of endosulfan toxicity in workers in a chemical factory. Poisoning occurred as they filled bags with the insecticide, neglecting protective clothing and masks. The symptoms appeared rapidly, within one to two hours in the lethal cases, and included initially headache, restlessness, and increased irritability, followed by vertigo, stupor, disorientation, and epileptiform convulsive seizures. In the workers that died, there was also loss of consciousness, cyanosis, dyspnea, foaming at the mouth, and noisy breathing (Israeli, et al. 1969). It was noted in a later report (Tiberin, et al. 1970) that there were pathological changes on the electroencephalograms. Hyperventilation improved the EEG picture.

CRITERION FORMULATION

Existing Guidelines and Standards

The National Technical Advisory Committee on Water Quality Criteria (USDI, 1968) did not establish a permissible limit of endosulfan in raw surface waters for public water supply purposes. The Committee stated, however, that the 48-hour TL_m (median tolerance level) of endosulfan to shrimp is 0.2 µg/l and therefore classified endosulfan as acutely toxic to shrimp at concentrations of 5 µg/l or less. On the assumption that 1/100 of this level represents a reasonable application factor, the Committee recommended that environmental levels of endosulfan should not be permitted to rise above 0.05 µg/l. This level is so low that endosulfan should not be applied directly in or near the marine habitat without danger of causing damage.

In the 1972 report of the Committee on Water Quality Criteria (National Academy of Sciences/National Academy of Engineering, 1972), a maximum concentration of 0.003 ug/l of endosulfan is recommended for whole (unfiltered) fresh water sampled at any time and at any place. This concentration was determined by multiplying the acute toxicity value of endosulfan for the most sensitive native aquatic species (rainbow trout, *Salmo gairdneri*) (Schoettger, 1970) by an application factor of 0.01. The marine criterion of 0.001 ug/l was similarly determined using LC_{50} values of the most sensitive marine species (striped bass, *Morone saxatilis* (Korn and) Earnest, 1974).

Revision of the above recommended standards may be indicated by more recent data. For example, the 96-hour LC_{50} value of 0.04 µg/l on pink shrimp (*Penaeus duorarum*) would, if incorporated, reduce the saltwater criterion from 0.001 µg/l to 0.0004 µg/l, using a theoretical application factor of 0.01 (Schimmel, et al. 1977). This theoretical ratio is used in the absence of an empirically derived factor. Macek, et al. (1976) have empirically derived application factors from their work on two fresh water species, fathead minnows (*Pimephales promelas*) and water fleas (*Daphnia magna*). The seven-day incipient LC_{50} of 0.86 µg/l and the maximum acceptable toxicant concentration (MATC) limits of 0.20 to 0.40 µg/l for fathead minnows give a derived application factor (ratio of chronic toxicity to acute or subactue) range of 0.23 to 0.47. MATC limits are the highest concentration for which there is no effect and the lowest concentration showing an adverse effect. The 48- hour LC_{50} of 166 µg/l and the MATC limits of 2.7 to 7.0 µg/l for *Daphnia magna*, however, give a derived factor range of 0.016 to 0.042.

The recent National Academy of Sciences report on drinking water did not address water standards for endosulfan (NAS, 1977).

Current Level of Exposure

Endosulfan has been detected in water samples from the United States and Canada. Maximum values reported from various studies include:

0.02 μg/l in streams of the western United States (one positive sample out of 546).

0.032 μg/l in drainage ditches from treated agricultural fields near Lake Erie.

0.011 μg/l in Canadian water systems.

0.083 μg/l in Ontario municipal water samples.

0.014 μg/l in surface and bottom water samples from Lake Erie.

The detection limit for endosulfan in water, using electroncapture gas chromatographic methods, is ~0.005 μg/l (Schulze, et al. 1973).

0.060 μg/l in the St. Lawrence River.

Residues in food (α-endosulfan, β-endosulfan, and endosulfan sulfate) result from the use of endosulfan on over 60 food and nonfood crops.

During the 1965 to 1970 period, daily U.S. intake of endosulfan residues was estimated using market basket samples from the total diet program of the FDA. These samples showed a daily intake of endosulfan (α-, β-, and sulfate) of from <0.001 to 0.001 mg/day.

The acceptable daily intake of endosulfan (i.e., the daily intake which during an entire lifetime appears to be without appreciable risk), as established by FAO/WHO, is 0.0075 mg/kg. This value corresponds to an intake of 0.525 mg/day for a 70-kg person.

Endosulfan has also been shown to bioconcentrate in the tissue of aquatic species. Bioconcentration data are summarized in Table 12.

TABLE 12

Summary of Bioconcentration Data for Endosulfan

Test species	Measured water concentration (mg/liter)	Exposure period (days)	Bioconcentration factor[a]	Source
Common mussel (*Mutilus edulis*)	1,000	70	22.5	Roberts (1972)
	100	14	28.5[c]	Roberts (1975)
	0.14[b]	-	600	Ernst (1977)
Scallop (*Ghlamys opercularis*)	100	14	25.7[c]	Roberts (1975)
Pink shrimp (*Penacus duorarum*)	0.089	4	0	Schimmel, et al. (19
Grass shrimp (*Palaemonetes vulgaris*)	1.75	4	245	Schimmel, et al. (19
Mullet (*Mugil cephalus*)	0.32	4	1,344	Schimmel, et al. (19
	0.035	28	2,755 (2,429)[d]	Schimmel, et al. (19
Spot (*Leiostomus xanthurus*)	0.076	4	895	Schimmel, et al. (19
Pinfish (*Lagodon rhomboides*)	0.15	4	1,299	Schimmel, et al. (19
Goldfish (*Garassius auratus*)	1	5	400	Gorbach (1972)

[a] Highest bioconcentration factor reported by the respective investigators. Whole body basis unless otherwise noted.

[b] -Endosulfan steady-state concentration; initial concentreation was 2.05 ug/liter.

[c] Based on summated values for separate tissues.

[d] Edible tissue.

Endosulfan residues (α-endosulfan, β-endosulfan, and endosulfan sulfate) have been detected in most types of U.S. tobacco products in recent years. The following data summarize the average residue levels (milligram residue per kilogram processed tobacco) detected in several independent studies.

	Year	Average residue (mg/kg)	Source
Cigarettes	1971	0.2	Domanski, et al. (1973)
	1972	0.38	Dorough and Gibson (1972)
	1973	0.83	Domanski, et al. (1974)
Cigars	1971	0.4	Domanski, et al. (1973)
	1972	0.41	Domanski and Guthrie (1974)
	1973	0.37	Domanski, et al. (1974)
Little cigars	1971	0.4	Domanski, et al. (1973)
	1973	0.22	Domanski, et al. (1974)
Smoking tobacco or pipe tobacco	1971	<0.2	Domanski, et al. (1973)
	1973	0.37	Domanski, et al. (1974)
Chewing tobacco	1971	0.2	Domanski, et al. (1973)
	1973	0.36	Domanski, et al. (1974)
Snuff	1971	<0.2	Domanski, et al. (1973)
	1973	<0.12	Domanski, et al. (1974)

Air samples from 16 states in 1970 showed an average level of 13.0 ng/m^3 α-endosulfan and 0.2 ng/m^3 β-endosulfan. None of the air samples collected in 1971 or 1972, however, contained detectable levels of either isomer.

Special Groups at Risk

Data on the presence of endosulfan residues (α-endosulfan, β-endosulfan, and endosulfan sulfate) in food, tobacco, water, and air have been briefly summarized in the preceding subsection. These data indicate the following three human populations that are at risk of exposure to endosulfan:

(1) Exposures occur primarily from: residues in foods as a result of the use of endosulfan on food crops and feedstuff; bioconcentration in aquatic species; residues in air adjacent to sites of manufacture or application; and residues in water.

(2) Residues in processed tobacco products (cigarettes, cigars, snuff, etc.) result from the field use of endosulfan.

(3) Dermal and respiratory exposure can occur during manufacture, formulation/packaging, field application, and harvesting.

Basis and Derivation of Criterion

Establishing a scientific basis for evaluating the hazard of endosulfan to man is difficult. At very high levels of acute exposure, humans show central nervous system (CNS) symptoms and may die. Several studies report endosulfan has been used for suicides (Terziev, et al. 1974; Couteslinis, et al. 1978). Workers who failed to use good safety practices (i.e., to cover skin and use respiratory protection) have died from endosulfan exposure (Israeli, et al. 1969). In one incident, three persons exposed showed CNS symptoms; two of them died. It therefore appears that the most toxic potential effect to man is that of CNS toxicity since the available data indicate a lack of carcinogenic, mutagenic, or teratogenic potential. The absence of reports on toxic effects associated with the proper use of endosulfan (particularly such effects as skin sensitization or other human symptoms) has been noted (Hoechst, 1966).

There appears to be considerable species variation in toxic effects. Of the species tested with endosulfan, cattle are the most sensitive to the neurotoxic effects and would therefore be a "worst case" model for human toxicity. There are much more controlled toxicity data on rodents, but cattle appear to be closer in sensitivity and effects to man. Data on CNS toxicity to cattle are presented in Table 13.

The relevance of these high exposure levels to a water quality standard presents additional sources of calculation error. The CNS toxicity in these studies is an acute symptom of high exposure. All reported human poisonings, however, have resulted from accident, human error, or suicidal intention. The reported poisonings of man and the most sensitive other mammal, cattle, have occurred after acute, high level exposure to concentrated endosulfan. These levels will not occur in drinking water. The key question then is, are there any data in the toxicology reports or studies to indicate that CNS effects can occur after chronic, very low level exposure to endosulfan?

Tiberin, et al. (1970) reported occasional EEG alteration in one of three men one year after a convulsive seizure following exposure to endosulfan. Terziev, et al. (1974) report that autopsy on an endosulfan suicide case showed "changes in the neurons" among lesions in other organs. Rats, although more resistant to toxicity than man or cattle, demonstrate no histopathological changes in the brain after receiving high doses of endosulfan orally for 78 weeks, or most of a lifetime (Weisburger, et al. 1978).

TABLE 13

Lethality and CNS Toxicity of Endosulfan in Cattle

Dose, route	Number animals exposed	Time to CNS toxicity (hours)	% Exposed showing CNS effects	Time to death (days)	% Exposed dying	Source
12.5 mg/kg, oral	2	10	100	6	50	Li, et al. (1970)
0.12% formulation, dermal	250	5	20	1	4	Thompson (1966)
4% dust, dermal	5	2	100	1	80	Nicholson and Cooper (1977)
35% powder, dermal	30	5	Apparently 100%	Hours to days	50	Braun and Lobb (1976)

Cerebral hemorrhage was reported in seven female rats that died early in the study (week 21) but the absence of lesions at even higher and more long-term dosage suggested to the authors that these deaths were not compound-related. Several lesions were present in the male rats and mice that died early in these endosulfan feeding studies. The most prevalent lesions included nephropathy, parathyroid hyperplasia and testicular atrophy, all without clear dose response pattern (Weisburger, et al. 1978).

An important question is "Do the apolar metabolites of endosulfan remain in the body to produce chronic effects if endosulfan is ingested in low level quantities over a long term?" No controlled metabolic studies in man have been reported, although Demeter and Heyndrickx (1978) report that endosulfan sulfate is a metabolite in humans. This metabolite is approximately as toxic to mice as the parent isomers (Dorough, et al. 1978), but no specific CNS effects were reported (based on toxicity trials on the pure compound).

The toxicity of endosulfan is somewhat greater in animals with deficiencies of dietary protein (Boyd and Dobos, 1969; Boyd, et al. 1970). The differences in even a dose as high as an LD_{50} are not great enough, however, to ascribe any potential human hazard to this mechanism or to suggest that protein-deprived humans would be more sensitive to chronic exposure to endosulfan in drinking water.

It can be concluded that (a) the controlled studies uniformly report CNS toxicity following acute high level exposure and (b) there has been no indication reported of specific lesions in mammals related to mortality following chronic exposure.

A water quality criterion could be based on the lowest no-effect level (NOEL) reported for endosulfan in test species. Available data on no-effect levels are summarized in Table 14.

The lowest NOEL reported in the published literature is 2.0 mg endosulfan per kilogram feed when fed to mice for 78 weeks (Weisburger, et al. 1978). This dose corresponds to 0.4 mg endosulfan/kilogram body weight per day for a typical 25 gram mouse consuming 5 grams feed/day:

$$\left(\frac{2.0\text{ mg endosulfan}}{1{,}000\text{ g feed}}\right)\left(\frac{5\text{ g feed}}{\text{mouse-day}}\right)\left(\frac{\text{mouse}}{0.025\text{ Kg}}\right) = 0.4\text{ mg/kg/day}$$

Applying a 0.01 animal to human uncertainty factor to this dosage gives an upper limit for nonoccupational daily exposure (ADI) of 0.28 mg/Kg body weight for a 70 Kg person:

$$\left(\frac{0.4\text{ mg}}{\text{Kg-day}}\right) \quad (0.01) \quad \left(\frac{70\text{ Kg}}{\text{person}}\right) = 0.28\text{ mg/day}$$

For the purpose of establishing a water quality criterion, human exposure to endosulfan is considered to be based on ingestion of 2 l of water and 18.7 g of fish/day. The amount of water ingested is approximately 100 times greater than the amount of fish consumed. The fish bioaccumulation factor for endosulfan, has been established to be 28.

The equation for calculating the criterion for endosulfan content of water is:

$$(2)\ (X) + (0.0187)\ (F)\ (X) = ADI$$

where: 2 = amount of drinking water was consumed, l/day

X = endosulfan concentration in water, mg/l

0.0187 = amount of fish consumed, Kg/day

F = bioaccumulation factor, mg endosulfan/Kg fish per mg endosulfan/l water

ADI = limit on daily exposure for a 70 Kg person

For $F = 28$

$$2X + (0.0187)\ (28)\ (X) = 0.28$$

$$2.52X = 0.28$$

$$X = 0.11 \text{ mg/l or } \sim 0.1 \text{ mg/l}$$

Consideration of dietary endosulfan levels (apparently 0.01 mg/day or less) and other sources of exposure (ambient levels, cigarette smoke, etc.) does not significantly affect this calculation.

In summary, based on the use of chronic toxicologic test data for mice and an uncertainty factor of 100, the criterion level for endosulfan is 0.1 mg/l. Drinking water contributes 79 percent of the assumed exposure while eating contaminated fish products accounts for 21 percent. The criterion level can alternatively be expressed as 0.5 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

TABLE 14

No-Effect Dose Levels for Endosulfan on Different Species and Biochemical Parameters

Species	Organ/Tissue	Effect Observed	No-effect dose	Route administered[a]	Source
Rats	-	Lethality	~55 mg/kg = LD_0	Acute Oral (Intragastric)	Boyd and Dobos (1969)
Rat	-	Lethality	40 mg/kg = LD_0	Acute Oral	Truhaut, et al. (1974)
Rat	Liver	Cholinesterase inhibition	68 mg/kg minimum	Acute Oral	Truhaut, et al. (1974)
Rat	Liver	Microsome enzyme function	50 ppm diet	Diet (2 weeks)	Den Tonkelaar and Van Esch (1974)
Rat	Embryo	Teratogenicity	10 mg/kg	Oral (Gestation Day 7-14)	Gupta, et al. (1978)
Rat (female Osborne-Mendel)	-	Lethality	445 ppm diet	Diet (78 weeks)	Weisburger, et al. (1978)
Hamsters	-	Lethality	70 mg/kg	Acute Oral	Truhaut, et al. (1974)
Hamsters	Liver	Enzyme inhibition: GPT, LDH	134 mg/kg minimum	Acute Oral	Truhaut, et al. (1974)
Mice	-	Weight depression	3.2 ppm diet	Diet (6 weeks)	Weisburger, et al. (1978)
Mice (Female B6C3F1)	-	Lethality	2.0 ppm diet	Diet (78 weeks)	Weisburger, et al. (1978)
Rabbit	Eye	Inflammation and irritation	1:1,000 aqueous	Instillation	Hoechst (1967a)
Rabbit	Eye	Inflammation, irritation	20% aqueous solution	Instillation	Gupta and Chandra (1975)
Rabbit	Skin	Irritation	100 mg/kg	Dermal	Gupta and Chandra (1975)
Chickens	Egg	Hatchability	0.07 mg/egg	Yolk injection	Smith, et al. (1970)
Dog	-	Gross and microscopic lesions	0.75 mg/kg/day	Oral (52 weeks)	FMC (1967)
Salmonella typhimurium	Strains TA98, 100, 1534, and 1978	Base-pair substitution (mutagenicity)	1.0 mg/plate	-	Dorough, et al. (1978)

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[a] Single dose unless otherwise noted

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